

Rothschild's Cat for all Pigeons

THE publication of the Rothschild and Dainton Reports (see page 169) marks the beginning of yet another period of heart-searching about the organization of British science. The chances are that the process will on this occasion be a good deal less gentlemanly than in the past—even the fierce arguments which there were about the Trend Report, which appeared in 1963, will by comparison appear like academic squabbles. For on this occasion, at least if Lord Rothschild has his way, blood will be spilled.

Both documents are organizational in the sense that they describe new frameworks within which the relationships between existing units may be re-adjusted. The Dainton proposal is, however, strictly passive—the Council for Scientific Policy which at present advises the government on policy in civil science would be replaced by a stronger body, called provisionally a board, with executive responsibility (to the Department of Education and Science) for apportioning funds between the research councils and, in the course of time, for creating new research councils or for abolishing those which have outlived their usefulness. In such a setting, so the Dainton argument goes, it would be possible for the research councils to evolve a more natural and dynamic balance between themselves. Lord Rothschild's proposals for the framework for the research councils are superficially similar but qualitatively quite different, for they introduce the concept, unfamiliar in Britain, that at least a part of what the research councils have to spend on civil science should be in the gift of the government departments most likely to benefit from whatever applied research the councils are asked to undertake. Obviously there is plenty of scope, in such a setting, for research councils to find themselves left high and dry for lack of work.

Now that both documents can be read side by side, it remains a mystery that the government has so stolidly refused to publish the Dainton Report. What it says is what everybody knows it would have said—that there is a case for the doctrine that government departments should continue to sponsor the research in whose applications they have a direct interest, and that the research councils should shoulder more distant responsibilities. With this premise, the notion that the Council for Scientific Policy should be replaced by a stronger body is sensible enough—that step should have been taken years ago, when it first became apparent (in 1967) that the council lacked the power to act and the time to talk. So why has the government risked alienating the research councils and the scientific community by declining to publish the Dainton Report before the Rothschild Report was ready? The fear that too many people might be publicly committed to the wrong policies can hardly have been serious.

What the government and Lord Rothschild have overlooked is that, for better or worse, the research councils and their constituents (many of whom sit on the 128 advisory committees whose number Lord Rothschild scorns) have been working towards a clubby relationship within which the scientific community has been able to enjoy the sense—or perhaps the illusion—that most

decisions were wise and all of them were fair. It will be a great loss if there should now evaporate the research council spirit in which normally sceptical and even suspicious people have been able to trust each other to make disinterested decisions even about the spending of money. The three Christmassy months which the government has now set aside for "wide public debate" will not go far to banish the sense that there is a shotgun solution in the offing (and there is a budget due four months from now).

That said, it is also fair to say that the Dainton Report does not come near to grasping the nettle which has grown up in the past few years about the research councils. Since the Second World War, the budgets for civil science have grown consistently faster than the Gross National Product and all other indices of economic performance. What used to be small and insignificant has grown to be large (a fifth of all public expenditure on research and development is spent by the research councils) and crucial to the health of many branches of national life—university research, for example. Is it any wonder that governments have begun to ask for proof that the research councils can justify their existence and the cost thereof? It is not so long ago that Sir Solly (now Lord) Zuckerman was advocating the abolition of the research councils on the grounds of demonstrable effiteness. The Dainton Report says that the Council for Scientific Policy undertook the review which it has now completed because of a proposal to transfer the Agricultural Research Council to the Ministry of Agriculture, Fisheries and Food. "The proposal had not previously been discussed with the CSP, who felt that no sufficient case had been made for what appeared to them to be a fundamental and ill-advised change." In the genteel language of government reports, this is fighting talk. It remains an awkward question whether the Dainton Report would ever have provided a sufficient defence of what it calls the research council principle.

A large part of the trouble is that the Dainton Committee has been trying to defend both the research council principle and the details of how it is at present applied. In reality, however, there are a good many places at which the present pattern of research activity could be changed without serious damage. It is, for example, no accident that the Agricultural Research Council should have been the occasion for the Dainton review—quite a large proportion of the research carried out by that estimable body is applied research in the sense that it is intended to be of direct benefit to people such as farmers and those who consume the food they grow. In its time, to its credit, the Agricultural Research Council has been fond of boasting about the way in which its work brought benefits to agriculture. Although a good deal of the council's work is strictly basic research which should not be harmed in any reorganization, it is increasingly hard for the Dainton Committee at this stage to fend off the question why the intended beneficiaries should not have a more direct say in the planning of likely benefits.



It is also hard to see why the Dainton Committee did not put forward more positive proposals for the reorganization of the research councils. To be sure, there is much to be said for providing a framework within which a suitable organization can evolve, but one of the most obvious defects of the system which now exists is that some of the research councils are demonstrably better able to justify a claim on public resources than are others. The Science Research Council has an essential role in higher education, while the Social Science Research Council has an important intellectual job to do in trying to cultivate respectable social science in Britain. Both the Medical and Agricultural Research Councils are divided between basic and applied research, with the basic research less well connected with the universities than it might be, sometimes because the universities play dogs in the manger. The Natural Environment Research Council, by comparison, spans a diversity of interests and objectives which are often indistinguishable from the interests of the other councils. In the circumstances, it would have been a powerful argument in its favour if the Dainton Committee had been able to suggest some of the ways in which the new supervisory board might have set about the removal of some of the anomalies which at present tarnish the research council principle as it is called.

To say all this does not imply that Lord Rothschild's proposals are the only alternative. To be sure, they do ingeniously provide a way in which three of the five research councils can marry basic and applied research, financing the first from what they can wheedle from the Department of Education and Science and the second from the government departments that would act as customers under the new regime. The difficulty, of course, is that nobody can be sure how this would work in practice. Undoubtedly it would be good for the departments if some of the cockiness of the research councils were to rub off in the more sober corridors of what passes for power in the Scientific Civil Service. At the same time, there is a danger that the departments would use the freedom which the Rothschild proposals would give to build up their own research establishments at the expense of perfectly good establishments now in the control of the research councils. Why, for example, should the Ministry of Agriculture pay the Agricultural Research Council for research on plant breeding when it can expand those of its own establishments already active in the field?

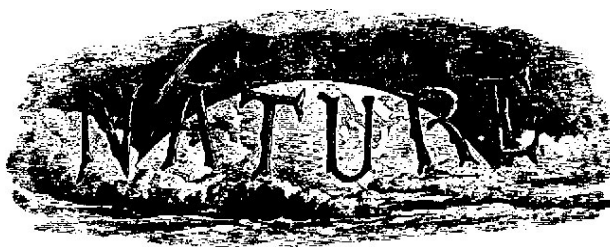
A more serious objection to the particular scheme which Lord Rothschild has put forward is that it would tend to institutionalize some parts of the pattern of research within the research councils. The Dainton Committee is, after all, correct in saying that the research council system is flexible and that it could be made more flexible. Once departments are blessed with a block grant for research each year, there is a danger that it will be harder to raise fresh money for applied research in novel fields. But the Rothschild proposals offer no solution to problems such as that posed a week ago by the House of Commons Select Committee on Science and Technology—how best to spend large sums of money on applied research of a kind likely to benefit the computer industry? The failure of the Rothschild Report to deal with questions like this—the questions on which Mr Anthony Wedgwood Benn's green paper foundered two years ago—is one of its most obvious weaknesses.

Another is that defence research appears to have been outside the scope of the inquiry.

In the circumstances, it is hard to predict just how the debate will go. The government has endorsed the doctrine of customer and contractor, but that is entirely understandable and in part, at least, something of a formality. Because the future of the Agricultural Research Council is now acknowledged to be the occasion for the present flurry of reorganization, it would be good to think that before the issue is finally decided, it will be more readily apparent how the proposed schemes for reorganization would affect the detailed operation of that research council. Precisely how has Lord Rothschild calculated that £14.5 million of the present budget might be transferred to the Ministry of Agriculture? That is the information needed in the weeks ahead if the wide debate is not going to be a wild sparring match.

It is also important that any new scheme for the administration of civil science should be tried out cautiously. This is a scientific issue, and a few experiments would not be entirely amiss. After all, a good deal of experience would be needed on both sides before the putative customers in the government departments would be able accurately to formulate their demands, and before the contractors in the research councils would be able to respond perceptively. So is it not clear that the first step in implementing Lord Rothschild's scheme should be a carefully controlled attempt to hive off to the Ministry of Agriculture financial responsibility for some (but not all) of the Agricultural Research Council's present responsibilities in applied research? For all their faults—and there are not many—the research councils play too important a part in British scientific life to be dealt with precipitously. But such a change, on a modest scale, would be a useful experiment even for the Daintonites to encourage.

100 Years Ago



M. JOLY, a distinguished member of the French Academy of Medicine, has recently read a paper before that learned society, in which he attributes the enervation of the nation, as evinced during the late war, to the combined effect of alcohol and nicotine upon the national character. "Tobacco," says Dr. Joly, "although of only recent introduction, has gained upon its older rival. Imitativeness and 'moral contagion' have done their work, until the use of this poison has penetrated everywhere—has enslaved the nation, caused personal and racial degeneracy, enervated the entire army, and made it slow to fight and powerless in action. The use both of spirits and tobacco has frightfully increased, and human depravity could scarcely devise a worse compound than the mixture of brandy and tobacco, which is the latest liquid novelty patronised by Parisian sensualists. The French consume more tobacco than any other nation."

From Nature, 5, 89, November 30, 1871

OLD WORLD

EUROPEAN LABORATORY

Italians Show Willing

THE working party set up by the Italian delegation to Esro to make recommendations on the future of the European Space Research Institute (Esrin) has produced a comprehensive plan which will be debated in Paris at an Esro council meeting within the next fortnight. The plan, which is a viable alternative to closing the laboratory, has the added advantage over its predecessor (see *Nature*, 234, 3; 1971) of having the support of the scientists at Esrin.

The first Italian plan involved splitting the laboratory into an Italian part and a part that would remain under the auspices of Esro, but it is now suggested that there should be cooperation between Esro and the Italian government without a physical division.

According to the new scheme, Italian scientists would be recruited to Esrin but would not exceed 50 per cent of those already employed. The result would be to concentrate Italian research in plasma and space physics and, indeed, under this scheme now put forward, the contribution of the Italian government — through the Centro Nazionale delle Ricerche (CNR)—would come from money saved in the rationalization of their research.

Under this plan, the budget of the reconstituted laboratory would be \$2.7 million of which CNR would contribute \$1.7 million and Esro the remainder. The property, under this plan, would still be owned by Esro.

Scientists at Esrin seem to be pleased with the plan but, even so, it is clear that the Italian proposal does not meet the original objections to the laboratory—that it carried out research which is incompatible with the present aims of Esro. Financially, the laboratory has been a modest burden—the total Esro scientific budget is \$63 million in 1971, but Esrin costs only \$2 million a year. Thus the argument that Esrin can still be maintained at a reduced cost to Esro of \$1 million does not remove the fundamental objection to the laboratory.

COMPUTER SOCIETY

Expanding into the Red

THE British Computer Society is planning to raise its membership subscriptions (which range at present from £3 for a student to £12 for a fellow) by a "substantial amount" according to Professor A. S. Douglas of the London School of Economics, who was elected president of the society at its recent annual general meeting. The reasons

for this are clear from the annual report published in the September issue of *The Computer Bulletin*; the society showed a deficit of £4,608 for the financial year 1970–71 compared with a surplus of £8,950 the previous year. Fortunately the reserve fund stands at about £50,000.

Although the society says that inflation has contributed to the reversal of fortune, it also emphasizes the expansion which has taken place during the past year, including, for example, the equipping and staffing of a print room for the production of the society's ever-increasing output of literature on conferences and computer education. The income from conferences and symposia was only about £2,000 during 1970–71 compared with about £6,000 the year before and this reduction seems to have been due chiefly to a change in the pattern of attendance at the society's marathon Datafair conference—more delegates attended than in 1970 but for shorter periods.

Although membership of the society has increased by more than 10 per cent to about 17,000 since a concerted recruitment campaign was started in May this year, Professor Douglas says that the rate of increase was not as great as had been hoped. About 50 new members a week are now being recruited and the society is aiming for a membership of about 30,000 within two or three years (see *Nature*, 231, 74; 1971).

University Grants Committee

MRS MARGARET THATCHER, Minister of Education and Science, announced in the House of Commons last week that she was increasing the universities recurrent grant for the 1971–72 academic year from £225 million to £238.1 million. The increase, according to Mrs Thatcher, is to take into account price increases during the past twelve months but Mr Norman Buchan, member for West Renfrew, disputed this as he thought a 6 per cent increase was insufficient to meet the effects of inflation. Mrs Thatcher also added that the provisional grant for the 1972–73 academic year would be £248.5 million, a sum that includes £1.7 million for running the computers which the UGC will take over from the Computer Board for Universities and the research councils. As well as this increased sum for university spending next year Mrs Thatcher announced that she was allocating an extra £23.25 million for equipment.

SPACE

Onward and Upward

A RECOMMENDATION that will be welcomed by the space science community in Britain is that an independent space agency be set up to be responsible to the Minister for Aerospace for all Britain's civil interests in space. This recommendation, made by the Select Committee on Science and Technology in their report published yesterday, will rationalize Britain's space effort which is now divided among several different departments (*United Kingdom Space Activities*, HMSO, £3.15).

The report is the result of a twelve-month effort by the committee that took evidence from people involved in space work in Britain together with evidence from the director-general of Esro and the secretary-general of Eldo. During the time that the committee sat Britain's space programme received setbacks with the scrapping of Black Arrow in July and the failure of the Europa II launcher recently, but there was part compensation, however, in the success of Prospero launched by Black Arrow last month. These ups and downs in Britain's space programme have had little effect on the committee's faith in the future of space activities, and it concludes that the future participation of Britain in space is "inescapable".

"Space should be used wherever necessary or preferable to alternatives as a means to help the broader ends of national policy." The committee feels it is this basic principle that should be followed by Britain, but it recognizes that Britain cannot compete with Russia and the United States. The committee feels that it is the government's duty to ensure that "through national and international space programmes our scientists, engineers and technicians are able to play a full part in advancing the frontiers of knowledge in space and developing their skills in space and its associated technologies".

The committee poses the question of whether Britain should reconsider participation in a European launcher project and so reverse the decision of 1968 when Britain stopped financial support for Eldo. The committee, after reviewing available European launchers, reluctantly concludes, however, that it will be best for Britain to continue its present policy of buying American launchers as required.

In a plea to keep the British space effort at its present level the committee stresses there should be no reduction in British space effort now that Black Arrow has been scrapped. The committee recommends that gaps that are at present evident in the National Space Technology Programme should be filled by the transfer of resources from

the defunct Black Arrow project. No worthwhile advances can be made in the development of space vehicles, according to the committee, unless there is a comprehensive research and development effort in the programme.

SCIENCE POLICY

France and Innovation

from *La Recherche*

THE Ministry of Industrial and Scientific Research launched a campaign to promote innovation, in Paris, on November 8, with a colloquium on "Innovation and Progress". About a thousand people took part, representing government, industry, universities and think tanks.

The central issue was naturally that of what can be done by the state and entrepreneurs to stimulate the innovative processes. As so often in meetings of this kind, very few really new ideas emerged. It was nevertheless significant that people from all walks of life gathered at an officially sponsored meeting to agree that France is engaged in serious technological competition. They also agreed that France lags considerably in the world technological race, and the various talks, debates and discussions were dominated by the significance of technical and commercial innovation in the process of total competition among industrialized nations. The immediate issues are how best to transform research into development, the role of small and medium enterprise in this process, and the need to create sources of venture capital to assure profitable innovation.

The three-day meeting was also an opportunity for the Ministry of Industrial and Scientific Research to publicize its own moves earlier this year to spur innovation. These measures are chiefly economic and seek to encourage innovation by way of fiscal relief. One of them eases the added-value tax structure at the point of licensing patents for processing and manufacturing techniques. Another smoothes the way for financial corporations which can invest in innovative enterprises by easing the amortization schedules affecting investment capital. There is yet another scheme to establish a public corporation using state funds to finance innovation.

Another goal of the conference was to provide a shop window for the setting up of a National Foundation for Innovation that will be aimed at invigorating research, disseminating information and organizing conferences on innovation.

Until recently, it was fashionable in France to talk about setting up scientific-industrial complexes, but the difficulties encountered recently by such complexes particularly in the United States, together with a lack of enthu-

siasm on the part of both industry and government in France, have taken the steam out of the concept. Both the government and business now realize that it takes more than good public relations to make this dream come true. Innovation has also been halted by gallic apprehension, as M. Duclos of the Société Montabert reminded his audience, that "Qui dit nouveau en France, dit suspect".

Some participants at the colloquium suggested that it takes more than a well organized meeting such as this to clear all the hurdles and avoid the pitfalls to innovation in a country like France. (Asked about the costs involved in organizing the colloquium, a ministry spokesman would only comment, "C'est très délicat.") Is meaningful innovation really possible in a society whose elite elements linger on, whose government-industry-university establishments will not communicate, and whose institutions remain essentially impervious to the seeping in of external influences? If the meeting had any merit at all, it was that of letting the French research and development world ask itself these very questions.

INDUSTRIAL RELATIONS

Stirring in the Ranks

IN spite of assurances to the contrary, the United Kingdom Association of Professional Engineers (UKAPE) is forming a Civil Service Division which hopes to be recognized by the Civil Service Department as the negotiating body for government engineers who are, at present, represented by the Institution of Professional Civil Servants (IPCS). This development springs from the complaint of some civil service engineers about IPCS representation. They claim that technicians are filling professional posts and, by their majority over professionals on committees, are denying the engineers an effective voice. As a result Mr Kenneth Peplow, general secretary of UKAPE, approached IPCS last year and suggested an affiliation between the two to give the engineers a stronger voice. When the proposal was rejected, the UKAPE formed its Civil Service Division in spite of the statement by Mr Peplow during negotiations that his association "would not try to usurp in any way the negotiation arrangements of your association".

Mr C. Cooper, deputy general secretary of IPCS, said this week that there is no basis for the complaints. He said that the engineers are part of the works group, which includes architects and surveyors, and are represented by a professional staffs committee—which has said that there is no place for UKAPE in the civil service.

Mr E. Pallant, the national organizer

of UKAPE's civil service division, said last week that the division was formed as the result of pressure from within the civil service rather than from the association's headquarters. He thinks that once the division is recognized by the Civil Service Department eighty per cent of engineers will join the association. As things stand, only some fifteen out of the 10,000 government engineers are committed to the division, but recruitment is due to start in the next few days. If sufficient numbers support the association it will apply for recognition to the Civil Service Department and, if it is refused, to the Industrial Court for a ballot under the Industrial Relations Act which could force the department—and IPCS—to recognize the division.

Mr Cooper describes this plan as "impossible" and says that if UKAPE thinks it will work "they are living in fairyland" as IPCS already represents engineers effectively and has a membership of 80 per cent among government engineers. Mr Cooper does not deny that engineers have problems over pay and careers but he hopes to see progress made when the new negotiations begin on January 1 next year—when IPCS, not the division, will be representing the engineers. Mr Cooper said that there are no doubt a few dissidents but there is no mass movement of engineers to UKAPE. "Their cause will not be advanced by dissipating their efforts," says Mr Cooper, "and the last thing we want is recruitment wars."

COMPUTERS

All Things to All Men

ALTHOUGH computer companies in Britain have reacted favourably to the Select Committee on Science and Technology's report on prospects for the British computer industry, there have

Royal Society Medals

THE three Royal Medals of the Royal Society for 1971 have been awarded to Dr G. Herzberg, National Research Council of Canada, for his "distinguished experimental researches in atomic and molecular spectroscopy and its applications in chemistry, physics and astronomy", to Dr M. F. Perutz, Medical Research Council Laboratory of Molecular Biology, for "pioneering work on the molecular biology and structure of proteins" and to Dr P. E. Kent, British Petroleum Company Ltd, for "distinguished contributions to oil and gas explorations and the geology of oil and gas fields".

been some misgivings about the criteria for purchase preference that have been proposed (see *Nature*, **234**, 117; 1971).

Sir John Wall, chairman of ICL, said this week that the report was a valuable contribution to the computer debate. He also pointed out that the Select Committee's "overall recommendations that imaginative support and preference should be given by the government to computer suppliers whose controlling interest is held by British nationals echo government policy expressed by Mr Frederick Corfield at the end of July 1971". ICL, he added, is well placed to meet the criteria proposed as a guide to purchasing preference.

Obviously hoping that the Computer Purchasing Board, if it is set up, would be able to interpret the purchasing criteria flexibly, Mr E. R. Nixon, managing director of IBM (UK) Ltd, said that he welcomes any proposals to increase competition for public sector business. "With two major manufacturing plants and a large development laboratory in Britain, IBM (UK) Ltd is, of course, already making a considerable contribution to the economy and, with its world wide experience of advanced applications to draw on, it is well placed to make a major contribution to the government's future needs." The sales of IBM (UK) Ltd were £170 million in 1970 compared with £131 million for ICL.

A spokesman for Honeywell was more critical of the report although he generally welcomed it and considered that it made some reasonable and firm proposals. Honeywell's chief complaint was that some of the recommendations in the report were incompatible with others. In particular it was not clear how the call for an end to the system of granting a single contract for a total system to one hardware manufacturer could be reconciled with, for example, the recommendation that preference should be given to suppliers whose controlling interest is held by British nationals—thus effectively ruling out all companies but ICL. The proposal to establish a Computer Purchasing Board has, however, met with Honeywell's approval on the grounds that the computer industry would then be dealing with the government through a single body. The proposal, Honeywell says, augurs well for greater consistency of treatment in the future and for a better understanding between the government and the computing industry. On the other hand, the company feels that the report does not spell out in sufficient detail how the recommended research and development support of £50 million should be distributed among British computer manufacturers; but it does consider that the setting up of a Computer Research and Development Board would greatly assist efforts to promote

REPRODUCTIVE BIOLOGY

WHO convenes Advisory Group

THE first meeting of the advisory group which is to help to direct the Expanded Programme of the World Health Organization on research, development and training in human reproduction was held in Geneva from November 22 to 26 (see *Nature New Biology*, **234**, 3; 1971). Invitations to attend the meeting were issued to: Dr B. Rexed, Public Health Services, Stockholm; Professor B. K. Adadevoh, University of Ibadan; Dr Lidija Andolšek, University Teaching Hospital for Obstetrics and Gynaecology, Ljubljana; Professeur Etienne Baulieu, Faculté de Médecine de Bicêtre, Paris; Professor Jack C. Caldwell, Australian National University; Dr Philip A. Corfman, National Institute of Child Health and Human Development; Professor Elsimar Coutinho, Universidade Federal da Bahia, Salvador; Dr A. B. Kar, Central Drug Research Institute, Lucknow; Dr Anne McLaren, Institute of Animal Genetics, Edinburgh; Professor William Paul, Toronto Western Hospital, Toronto; Dr Sheldon Segal, Rockefeller University; and Professor N. A. Yudaev, Academy of Medical Sciences of the USSR, Moscow.

common standards, both in hardware and software.

GEOLOGY

Abstracts Abandoned

GEOLOGISTS are concerned that the decision of the United States Geological Survey to end publication of *Abstracts of North American Geology* and *Geophysical Abstracts* next January will leave them without an effective and comprehensive English language abstracting journal. The decision seems to have been taken to avoid duplication of service, but the *Bibliography and Index of Geology* published by the Geological Society of America is not, according to Professor K. Clayton, University of East Anglia, an effective substitute for the doomed journals as it carries citations and key words but no abstracts. It also costs \$250 a year compared with \$10 a year for *Abstracts of North American Geology*.

There is at least some compensation for the geologists in that next January *Bibliographie des Sciences de la Terre* and the geology parts of *Bulletin Signalétique* will be combined to provide an expanded titles and key words service. There are also plans for the reconstituted journal to have input from the German government and from some East European countries. It is possible that some time in the future the Institute of Geological Sciences in Britain could provide a contribution but there are no plans at present to extend the journal to give a full abstracting service.

Next year there will be three chief English language abstracting journals that cover geology. *Mineralogical Abstracts* covers the fields of mineralogy, geochemistry and petrology, edited by Dr R. A. Howie of King's College London, and claims a 50 per cent coverage of all publications but a 90 per cent coverage of significant articles. There will also be two volumes avail-

able in the Geographical Abstracts series—*Geomorphology* and a new volume *Sedimentology*. Between them these journals only cover a part of the field and several important areas will not be abstracted effectively after the final publication the United States Geological Survey journals.

CHEMICAL INFORMATION

New Service Planned

THE United Kingdom Chemical Information Service (UKCIS) and the Institute for Scientific Information (ISI) are launching a new information service based on magnetic tapes which store data on the structure of new chemical compounds reported in the literature. The tapes are prepared each month by ISI but the service will be administered by UKCIS which is operated at the University of Nottingham by the Chemical Society. The existing facilities to subscribers offered by UKCIS depend upon data tapes compiled by the Chemical Abstract Service, which is partly financed by the American Chemical Society.

Each of the ISI monthly tapes contains data on about 12,500 new compounds, encoded in such a way that letters and numbers correspond to particular sub-structures (for example carbonyl and hydroxyl groups); this makes it possible for searches to be made for chemical sub-structures of particular interest to individual subscribers while also allowing recognition of overall structures.

Subscribers to the new service will receive monthly lists of relevant compounds, each associated with an abstract in the ISI publication *Current Abstracts of Chemistry*, which details references, synthesis routes and so on. The cost to subscribers will probably be between £70 and £120 a year, about the same as for the other services which are to continue as before.

NEW WORLD

How Far will this Special Action Office Go?

PRESIDENT NIXON's campaign against drug abuse, launched in his message to Congress in June this year, has become bogged down in congressional committees. Last week, the Senate Committee on Government Operations reported out a bill that differs in some important respects from Nixon's original intentions. The bill now goes to the Senate Committee on Labor and Public Welfare which also has an interest in its provisions. Meanwhile, in the House of Representatives, the Subcommittee on Public Health and Environment of the Committee on Interstate and Foreign Commerce is in the throes of marking up legislation after conducting exhaustive hearings on the bill. What was expected to be a quick passage through Congress has therefore become a long drawn out process, but both the White House and key congressmen involved in the legislation are confident that a bill will soon be ready for the President's signature.

In some respects, the delay in presenting the bill to the floor of the House and the Senate reflects the complicated nature of the differing philosophies over how to attack the problem of drug addiction. The nub of President Nixon's original proposal was the creation of a Special Action Office on Drug Abuse and Control within the Executive Office. The office would be responsible for directing federal efforts to rehabilitate drug addicts and directing programmes aimed at education on drug abuse. An important criterion was that the Special Action Office should not be concerned with law enforcement, since rehabilitation should be treated separately from the question of legal sanctions against drug users and pushers.

The Senate Government Operations Committee last week reported out a bill that extended the scope of the Special Action Office but clipped its powers. Essentially, the committee seeks to give the office the power to recommend to the President policies for the Bureau of Narcotics and Dangerous Drugs (part of the Department of Justice) but takes away from the director of the office the power to control and carry out programmes directly from the White House and to transfer money from one agency to another. In the original bill, President Nixon had given the office the power to regulate the budgets of the various federal agencies

that are devoted to drug rehabilitation and education, but the committee decided that his powers should be limited to providing overall policy direction of federal efforts in drug control with the power to modify budgets. The director would not, however, be able to take over the direction of individual projects.

Another important change put in by the committee is that the Special Action Office should have some limited direction over law enforcement and related

activities. The direction would in fact boil down merely to the offering of advice. The House Subcommittee on Public Health and Environment is now likely to report a similar bill to the main committee in spite of the conviction held by some members that the powers of the Special Action Office would not be addressed to one of the most important points—the international regulation of poppy growing and the smuggling into the USA supplies of heroin.

MARINER 9

First Results May Aid Russian Lander

As expected, the safe arrival of Mariner 9 in orbit around Mars (see *Nature*, 234, 67; 1971) has provided accurate data on the orbit of the planet and its gravitational field. These discoveries have provided the first opportunity for practical cooperation between the American team controlling Mariner 9 and the Russians guiding the progress of their probes Mars 2 and Mars 3.

On November 19 the following findings were announced from the Jet Propulsion Laboratory in California, control centre for the mission:

- A large bulge at the equator of Mars
- Gravitational anomalies which may be caused by martian mascons
- Water vapour present in the atmosphere over the south pole
- Surface temperatures ranging from 240 K at mid-afternoon to 200 K at night
- Uniform atmospheric temperature of 350 K from near the surface to a height of 40 km

In addition, the dust storm clouding the martian surface now appears to be clearing and surface features should soon be identifiable.

It seems that improved figures for the exact orbit and ephemeris of Mars have already been relayed to the Russians. These refine standard measurements by only a few kilometres, but the detailed information which is being gathered about the martian mascons could prove extremely valuable when the Russian probes come to attempt the soft landing which has been unofficially promised. Variations in the orbit of Mariner 9 caused by local irregularities in the

planet and by the large equatorial bulge cause changes in the craft's velocity of 2 to 3 millimetres per second, and produced an average 5 second change in the duration of its orbit during each of the first 8 revolutions. This slowing down by 40 s should be regained as Mariner 9 shifts away from the direct influence of the bulge, according to Dr W. O'Neill of the Jet Propulsion Laboratory.

The insertion of the spacecraft into orbit went smoothly, and required rather less fuel than had been allowed. The manoeuvre, which changed the orbit of the spacecraft so that periapsis (closest approach to Mars) is now 868 miles and takes place in the middle of the viewing period available to the Goldstone antenna tracking Mariner 9, left plenty of fuel for subsequent trim manoeuvres using the main engine, which is rated at 300 lb thrust but appears to be performing rather more efficiently.

Just how severely the strong winds seen whipping up the present dust storm on Mars might affect a soft landing can only be determined effectively by making a landing attempt. It does seem certain, however, that the Russians will wait for the storms to clear as much as possible before venturing such a step. Traditional Soviet secrecy makes it impossible to say just what is planned, but it is known that the NASA Viking lander, scheduled for 1974, will be able to wait for up to one month in Mars orbit if conditions are not immediately suitable for a landing on its arrival. With the Russian lander in prospect and Mariner 9 now in full scientific operation after orbital adjustments, the weeks ahead seem likely to produce the hoped for excitement after the necessary tedium of the long interplanetary journey.

SCIENCE POLICY

Two Views of British Science

THE British Government has at last published the report of the Dainton Committee and, for good and unexpected measure, the frequently conflicting report on the same subject which has been prepared by Lord Rothschild, the head of the Central Policy Review Staff (Cmnd. 4814, HMSO, £0.525).

The two documents appear within the same green cover, and the government says that although it endorses the principle laid down by Lord Rothschild that the relationship between government and the research councils should in future resemble that between customers and contractors, it says that it will not make detailed decisions about the proposed reorganization until there has been "wide public debate". The intention is that formal discussions with interested bodies such as the Royal Society should be completed by February 29 next year, but interested persons are invited to send their views to the Chief Scientific Adviser at the Cabinet Office before January 14.

The Rothschild report is a provocative document written in a kind of racy telegraphese. Its starting point is the view that there is no meaningful way of striking a correct money balance between pure and applied research. And in the proper organization of applied research, "the customer says what he wants, the contractor does it (if he can) and the customer pays".

Organizing the Customers

Although it is acknowledged as sensible that the Department of Education and Science should support basic research through the research councils and the University Grants Committee, Lord Rothschild complains that much of the research sponsored by the Agricultural, Medical and Natural Environment Research Councils is applied research, "with no customer to commission and approve it. This is wrong. However distinguished, intelligent and practical scientists may be, they cannot be so well qualified to decide what the needs of the nation are, and their priorities, as those responsible for ensuring that those needs are met."

In the context of government science, the customers are government departments. To enable them to decide which research and development programmes are necessary and how much should be

spent on them, the customers will need a Chief Scientist to formulate needs and a "Controller R & D" to administer the programme. In practice, the argument goes, it would be necessary to provide the officials concerned—who would work in parallel with each other—with staffs big enough to do the work required. The Rothschild report suggests that there should be a strict separation of capital and current expenditure on research and development.

Research Surcharge

One of the most novel proposals in the report is that it should be openly acknowledged that something like 10 per cent of the cost of applied research is at present properly spent on more basic work. Under the proposed arrangements between customers and contractors (the research councils and other government research establishments) there should be a "general research surcharge". The total amount available under this heading on the basis of current budgets would amount to no less than £54 million a year.

The Rothschild report's appraisal of the research councils is sceptical, to say the least. At the outset, the report raises the question whether it needs more than 1000 people, with salaries which exceed £4 million a year, and 128 advisory committees, to spend a total of £109 million (in the current financial year). "A review of these numbers is needed."

Lord Rothschild explains that the Science Research Council has been excluded from his review because only a little of the work it sponsors is applied research and that the Social Science Research Council has been excluded "because it is in its infancy". There has plainly been some dispute about the distinction between pure and applied research. Lord Rothschild says that the Council for Scientific Policy does not accept that there is an "unambiguous" distinction (in the sense of whether or not there is a customer), and goes on to ask that the government should "reject the view that there is no logical division between pure and applied research, a view that may be intended to protect the research councils from the imaginary ravages of applied R & D users."

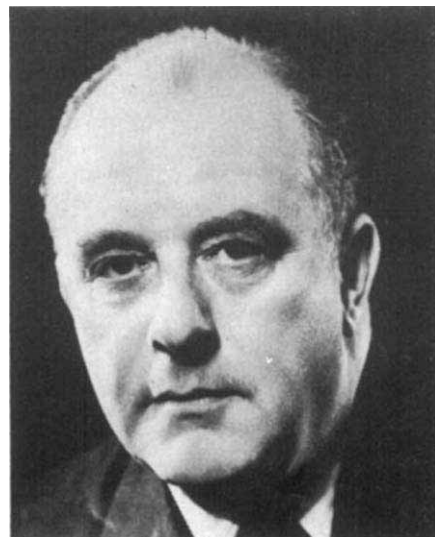
Department Satellites

With these reservations, Lord Rothschild would like to see the heads of the Agricultural Research Council (ARC), Medical Research Council (MRC) and Natural Environment Research Council (NERC) become the controllers of R & D for the appropriate government departments—the Ministry of Agriculture, Fisheries and Food, the Department of Health and Social Security and (for NERC) the Department of Trade and Industry and the Department of the Environment.

For practical purposes, the result



Sir Frederick Dainton



Lord Rothschild

would be that the three research councils would become satellites of one or more government departments. "The present division is both illogical and undesirable. It perpetuates meaningless or harmful distinctions between research and development, and panders to scientific snobbery—the 'haves' in the research councils and the 'have-nots' in the departments." The report suggests that each research council should have a whole-time chief executive and a part-time chairman.

Financing the Changes

Where will the money come from to support these activities? The nub of the recommendations is that a substantial part of the budgets of the three research councils under scrutiny should be transferred from the Department of Education and Science to the appropriate customer department. Numerically, something like £26.7 million out of the current budget for the research councils of £109 million should be re-allocated in this way. The exact amounts are shown in the table below.

What assurance could there be that the departments would not take their new-found money for research and development and place contracts with organizations other than the research councils? For the first four years, Lord Rothschild would impose some restrictions on the extent to which departments would be free to redeploy their resources. In the first year, there could be no reduction of the amount of business finding its way into a research council's hands, and in the succeeding years the amount could not be reduced by more than 10 per cent each year. "It is naturally for the departments to decide if they wish to increase their payments to the research councils".

Some of the salt which Lord Rothschild has rubbed into people's skin, wounded or otherwise, lies in the recommendations which he has to make about the Council for Scientific Policy. This, he says, should be reconstituted in such a way that the five chief executives of the research councils should be *ex officio* members, together with the chairman of the University Grants Committee, and that there should also be four independent scientists and a part-time chairman blessed by the president of the Royal Society. The chief function of the CSP should be to advise on the division of funds for the research councils which are not in the gift of customer departments. There is some dispute between Rothschild and Dainton (see below) on whether the president of the Royal Society should automatically be a member—Rothschild thinks not.

Lord Rothschild also flatly rejects the distinction between tactical, strategic and basic research which is the starting

point for the Dainton analysis. On strategic science, "work of general practical interest", the Rothschild report says that the names of the research councils "imply applications"—and that the philosophy of the Dainton report "should be rejected".

Lord Rothschild asks that the research councils should re-examine their policies of setting up research units around individual scientists and then of feeling free to close them down again if the person concerned should die, retire or move. On the need for long-term research, the report says that both the universities and the general research surcharge should help to make sure that departments do not sacrifice everything to immediate objectives, while it should be in the brief of government research administrators that variety is a necessary part of a healthy research programme. But with this reservation, "longer term research has no special merit or value in itself, and there is no positive correlation between the importance of a discovery and the time it took to make".

Price of Advice

The Rothschild report also has several detailed recommendations about the organization of the government's relations with the scientific community. It suggests that the British Government's annual subvention to the Royal Society should be paid by the Cabinet Office rather than by the Department of Education and Science. Lord Rothschild would like to see a rationalization of the payments made to the members of the research councils and the other scientific advisory bodies—the implication is that the £15.75 a day paid to independent members of the Council for Scientific Policy, and the £750 a year paid to the independent members of the Medical Research Council, is more than the same people would be paid for attending scientific advisory meetings elsewhere in government. "It is strongly recommended that this subject be examined or re-examined by the Civil Service Department, attention being paid to the duty of the citizen to render public service and to be remunerated with this in mind."

Lord Rothschild has strong things to

say about the need for more mobility between the scientific civil service and the rest of it. He deplores the meagre transfer from scientific to administrative posts, argues that movement through a laboratory is necessary for the maintenance of its scientific quality, and suggests that a start should be made "in the rectification of this organizational failure" by giving putative heads of government laboratories at least one year's experience in the administrative branches of the civil service.

The Chief Scientific Adviser to the British Government should, according to the report, provide himself with at least one biologist and one chemist within his present complement of four physicists, two mathematicians, one engineer and one economist. His function should be to warn departments of occasions when the research programme of one may have a bearing on that of another but, in this world in which the customer is supreme, there is no case for asking that the Chief Scientific Adviser should exercise a supervisory function.

Lord Rothschild does not so much reject the Haldane principle as reinterpret it. He says that the doctrine "is sometimes invoked to justify the independence of applied scientists from those who may benefit from the results of their work". He then provides a list of contradictory quotations from the report and concludes that the most commonly quoted form of the Haldane principle has "little or no bearing on the conduct and management of government R and D in the 1970s".

Dainton's Deliberations

The Dainton report begins with the acknowledgment that governments spend money on science only because they are "aware of the power of science to serve national goals". Avoiding the trap of classifying scientific work into "pure" and "applied", the committee distinguishes between three categories of research—tactical, strategic and basic. Basic research, in this definition, is intended as research and training with "no specific application" in view. Strategic research is the foundation for the day-to-day needs of government and industry for research and development. Like all

Reallocation of Research Council Budgets

Council	Present budget (£ million)	Transferred to department(s) (£ million)
SRC	50.9	0
SSRC	2.2	0
ARC	18.7	14.5
MRC	22.4	5.6
NERC	15.3	7.6
	£109.5 million	£27.7 million

previous lexicographers of science, the Dainton committee emphasizes the fuzziness of the boundaries between the three categories of science.

Most of the committee's work is concerned with the research councils which are at present the chief sources of funds for the support of civil science in Britain and the report says that it has deliberately set out to re-examine the old Haldane doctrine—the notion that research is most fruitfully applied to the needs of government when the agency responsible for research is separate from the government department most directly concerned. Although the report does little more than say that it is now necessary that there should be close links between policy formation and research, the fact that the committee has not endorsed the Haldane doctrine is in itself a sharp break with the precedents of previous committees on the administration of civil science in Britain. In the end, however, the committee comes out with what it calls a reaffirmation of the research council principle—to allocate the research councils to the departments which they might seem to belong would be inefficient and uneconomic.

The Dainton committee is, however, strong on the need for closer links between the research councils. On questions such as the balance of effort in civil science, the breaking of new and interdisciplinary ground as with pollution research and the organization of studies of scientific manpower, the committee considers that there needs to be closer coordination than in the past. At the same time, it says that it is improbable that the Council of Scientific Policy, which is an advisory organization, could be strengthened sufficiently to fill the bill.

For all these reasons, the committee says, there is a need for important changes in the present method of organization. The chief need is that

government departments should play a fuller part in the formation of scientific policy. "The principles of scientific responsibility and of judgment of scientific merit which are important characteristics of the research council system must, however, be preserved".

The committee mentions but rejects the proposal, much talked of in the past few months, that there should be a single research council responsible for the administration of all government subventions for civil science—such an organization would be too remote and too prone to error. Rather, the committee wishes to make the most of the sense of involvement with the formulation of scientific policy which, it says, is provided by the committee system under which the research councils operate at present.

This is why the committee comes out with the proposal that there should be a coordinating board consisting of the heads of the existing research councils which would be able to act as the direct intermediary between the Department of Education and Science and the research councils themselves. The board would naturally become, according to the Dainton committee, the chief source of scientific advice to the Department of Education and Science, and would in particular be responsible for settling such boundary disputes between the research councils as might arise. The committee suggests that the coordinating board should also be empowered to "add to or subtract from the number of research councils in response, for example, to the growth of new disciplines and the emergence of new professional groups. It should not, however, at any stage so reduce the number of research councils that the virtues of the specialist council were lost". This passage will be scanned with close attention by all those who may wish to use the publication of this report as an argument in favour of the abolition

or the retention of one or other of the research councils—the Agricultural and the Natural Environment Research Councils have been most at risk.

How will the new system make it possible for government departments other than the Department of Education and Science to have their say about the formulation of policy on research in the civil field? The suggestion is that the coordinating board should include as full members representatives of the departments most likely to be interested. "So as not to make the board too big," the committee suggests that the Cabinet Office should be represented, together with three other departments chosen in rotation. An important feature of this recommendation is that there should be independent members among whom the president of the Royal Society would be appointed as of right. The chairman of the University Grants Committee and at least one vice-chancellor should also be appointed.

The report says that the chairman of the coordinating board would be the key figure in the new arrangement, but that the board would also have to be provided with a secretariat sufficiently strong to shoulder a good deal of planning and administration. Within this framework, the Dainton committee seems to be in favour of a limited amount of reorganization of responsibility. It says that some of the work at present carried out by research councils could be transferred to an appropriate government department. On the other hand, it would like to see the new board assume responsibility for some departmental function such as the British Museum (Natural History) (at present under the direct control of the Department of Education and Science).

In short, the Dainton report turns out to be not so much a recipe for change as for a framework within which change might happen.

Table 1 Research and Development in Britain, 1961–1971

Sector providing funds	1961–62		1964–65		1967–68		1970–71 (estimates*)	
	£ million	Percentage of (4)	£ million	Percentage of (4)	£ million	Percentage of (4)	£ million	Percentage of (4)
Government support								
(1) Total civil	139.3	36.2	171.9	40.3	259.4	53.5	350.0	60.3
(2) "Research council" element in (1)	24.0	6.2	38.0	8.9	57.1	11.8	93.8	16.2
(3) Total defence	245.7	63.8	255.1	59.7	225.9	46.5	230.0	39.7
(4) Total civil and defence	385.0	100.0	427.0	100.0	485.3	100.0	580.0	100.0
	£ million	Percentage of (10)	£ million	Percentage of (10)	£ million	Percentage of (10)	£ million	Percentage of (10)
(5) Total civil and defence as returned by sectors carrying out the work	378.2	57.5	421.2	54.6	493.1	51.3	n/a	—
(6) Universities (own funds)	1.3	0.2	1.8	0.2	5.7	0.6	n/a	—
(7) Private industry and public corporations (including research associations)	266.2	40.5	311.6	40.4	405.2	42.1	n/a	—
(8) Funds from overseas	} 12.0	1.8	{ 20.8	2.7	30.3	3.1	n/a	—
(9) Other					27.8	2.9	n/a	—
(10) Total	657.7	100.0	771.4	100.0	962.1	100.0	n/a	—

* Figures in this column include expenditure overseas (estimated to total £40 million).

NEWS AND VIEWS

Gravitational Lenses and the Structure of the Universe

THERE are several possible ways of explaining the redshift of the emission lines observed in the spectra of quasars. The most obvious view, and the one that is most widely accepted, is that quasars are at cosmological distances, and that their redshifts are due to the expansion of the universe itself. Given the present values for the Hubble constant, H , and for the mean density, $\bar{\rho}$, of matter in the universe, one can then calculate the distances, L , to the various quasars. Admittedly there are uncertainties in H , and even more so in $\bar{\rho}$, and these introduce corresponding errors into the estimates for L . But in all cases it is found that the quasars are extremely distant objects, and that therefore they must emit energy at a prodigious rate. A luminosity of 10^{47} erg/s⁻¹ would be quite typical for a quasar; this is $\sim 10^4$ times larger than the combined luminosities of all the stars in a normal spiral galaxy.

The alternative explanations for the quasar observations seem, at first sight, to avoid this conclusion and would save us from having to admit that such powerful sources of radiation exist. They fall into three categories and the alternative postulates are, first, that the quasars are not at cosmological distances but originated quite close to the galaxy in an explosive event which gave them their high velocities; second, that the redshift is gravitational and not due to the Doppler effect; and, third, that the redshift is cosmological but that the quasars are much less luminous than they appear to be. According to this theory their true brightness is overestimated because gravitational lenses in the intervening space have to some extent focused their radiation onto the Earth.

None of these alternative explanations has been very successful. The local theory puts us in an unacceptable, almost pre-Copernican position with respect to the rest of the universe for the Earth should have to be right in the middle of an expanding association of some 300 or more "quasars". But where are the corresponding associations surrounding at least some of the other galaxies? Surely some at least of the "quasars" belonging to these associations would have to be approaching the Earth, and would therefore have to be blueshifted. No such object has ever been found, a significant null result.

The second postulate, the gravitational theory, suffers from the drawback that it is hard to concentrate sufficiently a large enough mass to produce the necessary redshift. Masses can be suitably distributed to bring about such redshifts, but not for long. In general they are endangered by gravitational instabilities, with the consequent loss of the quasar into a black hole.

The only one of the alternatives left is therefore the gravitational lens theory. At first sight this seems to be the most improbable theory of all; indeed, just what is a gravitational lens? From relativity theory it is known that the presence of matter distorts the geometry of space. Radiation therefore does not travel in straight lines in the Euclidean sense. Any cosmological model is based on a geometry which allows for this effect, at least as far as the smoothed-out density distribution of mass in the universe is concerned. But this is not quite enough. Much of the matter in the universe is lumpy, rather than

smooth, and is concentrated into various hierarchies of condensations like galaxies, star clusters and stars. The radiation passing through or close to a condensation is deflected more than the average for the universe. The effect is analogous to refraction in optics; hence the term gravitational lens.

On page 199 of this issue of *Nature*, N. Sanitt assesses the importance of the gravitational lens effect on the radiation from distant sources. He discusses, in particular, what happens when the radiation travels past a model galaxy with suitably symmetrical properties. He then calculates the probability that an observer on the far side sees an image, intensified by a factor A , or more. Given a large enough value for A , say 10^3 , even a relatively modest source like the nucleus of a Seyfert galaxy might be mistaken for a quasar. The redshift of the spectral lines is, of course, unaffected by the focusing process.

Characteristically there is a probability proportional to A^{-2} that a gravitational lens would produce a magnification A , or larger. Other factors also enter the expression for the probability and it is assumed that there is no correlation between the positions of the source, the lens and the observer. But the theory has got off to a bad start, for one can only expect that, at best, one Seyfert in a million, with luminosity 10^{44} erg s⁻¹, will mimic a quasar the luminosity of which is a thousand times (or more) as great. What is known about the statistics of Seyferts argues strongly against the existence of an adequate number to account for all the quasars. So it is concluded that the straightforward interpretation was right, and that most quasars are really as bright as they appear to be.

At this stage should the study of gravitational lenses be regarded as a waste of time? To answer this, Sanitt's result must be reconsidered, and in particular the distribution of probabilities for magnification by a factor larger than A . The inverse square dependence that he finds is quite generally valid: it would equally well occur for a radiation field that had become distorted by encounters with a random distribution or arbitrarily shaped masses in the universe. The only proviso is that the source of the radiation must be sufficiently redshifted; gravitational lenses tend to have a large focal length and there is no important focusing effect for nearby objects. But gravitational distortions are bound to set in for sources beyond a certain distance and it is entirely possible that some of the quasars are far enough away.

Very large magnifications will still occur only rarely but it is profitable to discuss the influence of smaller changes. Small magnifications or demagnifications are far more likely to occur and may well confuse the statistics for the luminosities of distant compact sources. Just how much gravitational distortion occurs will depend on the total mass of the various condensations. The present inventory of the mass distribution in the universe is not complete enough to give a good estimate. In fact, there is much talk of "missing mass", for example in connexion with the problem of the equilibrium of clusters of galaxies. In principle the gravitational lens effect

provides a probe for detecting the various condensations of masses. It may yet turn out to be a very useful concept with interesting applications.

This experience with quasars leads to several more general conclusions. The first is that one must occasionally accept the commonsense interpretations of

striking observational results, even if they trample on cherished theories. The second is that quite often a theoretical study, undertaken for the wrong reasons, may turn out to be much more useful in unexpected ways. But most important it shows how science, like most other human activities, proceeds by trial and error.

Further Progress in Cholinergic Receptor Studies

SINCE the snake venom toxin α -bungarotoxin was reported to be a unique tool for the investigation of cholinergic receptor sites because of the highly specific manner in which it binds to such sites (Changeux *et al.*, *Proc. US Nat. Acad. Sci.*, **67**, 1241; 1970; Miledi *et al.*, *Nature*, **229**, 557; 1971), progress in this field has been rapid. Miledi and Potter (*Nature*, **233**, 599; 1971) last month reported the use of α -bungarotoxin in studies of cholinergic receptor sites in vertebrate muscle, and on page 207 of this issue of *Nature*, Barnard, Wieckowski and Chiu report the results of studies similar to those of Miledi and Potter, performed at the same time.

Barnard *et al.* used α -bungarotoxin which was radioactively labelled by acetylation with tritium labelled acetic anhydride. The labelling procedure was shown to have no effect on the pharmacological potency of the toxin in blocking acetylcholine effects at muscle cholinergic receptors. When labelled toxin was administered to mice or if diaphragm preparations were incubated *in vitro* a complete block in neuromuscular transmission resulted. The irreversible blocking effects of bungarotoxin were prevented if the reversible antagonist *d*-tubocurarine was present during exposure to toxin. The binding of labelled toxin to nerve-muscle preparations was also resistant to removal by repeated washings.

In preparations saturated with labelled toxin, autoradiographic studies showed a highly selective localization of the radioactivity over neuromuscular end-plates on the muscle surface. Quantitative autoradiography of end-plates labelled with bungarotoxin, or with the irreversible acetylcholinesterase inhibitor di-isopropylfluorophosphate (tritium labelled), showed that the densities of toxin binding sites and acetylcholinesterase active sites on the end-plate membrane were equal. These two types of binding site were shown to be independent, because there was no mutual inhibition of binding by the two labelling agents used if both were present together. The number of cholinesterase sites and toxin binding sites were equal, so that estimates of the number of toxin binding sites were made by β -track counting of end-plates labelled with ^{32}P -DFP. This gave values of 3.0×10^7 sites per end-plate in mouse diaphragm muscle, and values between 3 and 9×10^7 sites per end-plate in other mouse and chicken muscles. The value for mouse diaphragm is similar to the value of 1.6×10^7 bungarotoxin binding sites per end-plate reported recently by Miledi and Potter. Barnard *et al.* calculate that the density of toxin binding sites (that is to say, cholinergic receptors) on end-plate membranes is 12,000 per μm^2 , and the receptor sites and cholinesterase active sites together occur at a density of 1 protein sub-unit per 5,000 $\text{\AA}^2$ of membrane. This suggests that the enzyme and receptor molecules may be present as a fairly tightly packed mosaic in the end-plate membrane.

Barnard *et al.* have also estimated, by comparison of the time course of blockade of neuromuscular transmission and the time course of toxin binding to muscle, the proportion of receptor sites which must be blocked before any pharmacological blockade is observed. They show that no impairment of neuromuscular transmission occurred if about 50 per cent of the toxin binding sites were occupied by bungarotoxin, and that blockade thereafter became marked when about 70 per cent of the toxin sites were occupied. This suggests that the "spare receptor" population at mouse diaphragm end-plates may be considerably less than was suggested by the calculations of Miledi and Potter.

The identity in number of cholinergic receptor sites and acetylcholinesterase active sites reported by Barnard *et al.* in mammalian muscle has also been described in the electric organs of electric fish (Miledi *et al.*, 1971) and in electric eels (Changeux *et al.*, 1970). The significance of this stoichiometry in functional terms is not clear, but it may have important implications for the question of the origin of the esterase and receptor sites at neuromuscular junctions and at other cholinergic synapses. It has recently been suggested (Hall and Kelly, *Nature New Biology*, **232**, 62; 1971; Betz and Sackman, *Nature New Biology*, **232**, 94; 1971), that acetylcholinesterase may not be located in the muscle membrane, but rather in the basement membrane overlying the muscle surface. The identity of receptor sites with enzyme sites suggests, however, that the two macromolecules involved probably have a common biosynthetic origin, presumably within the muscle cells.

Further important progress in the characterization and isolation of cholinergic receptor sites is reported by Changeux, Meunier and Hutchet (*Mol. Pharmacol.*, **7**, 538; 1971), who worked with the cholinergic receptors in the electric organ of the eel, *Electrophorus electricus*. The snake venom toxins α -bungarotoxin, and the α -toxin of *Naja nigricollis* (a cobra venom with properties similar to those of bungarotoxin), were used as specific receptor binding agents, and were found to prevent the reversible binding of radioactively labelled decamethonium to electroplax membranes, and to solubilized preparations of these membranes made by treatment with deoxycholate. The use of equilibrium dialysis binding of a reversible agonist, decamethonium, as a method for detecting cholinergic receptor sites has certain advantages over the use of the irreversibly binding venom toxins. In the final analysis, receptor purification must make use of marker molecules which can easily be removed from the purified preparations—this is not the case with α -bungarotoxin which binds very strongly to the receptor sites.

Changeux *et al.* were also able to measure in a series of elegant kinetic experiments the binding constants for the

affinity of binding of agonists such as decamethonium and carbamylcholine, and antagonists such as *d*-tubocurarine, gallamine and the venom toxins. These studies establish the important point that the constants for the binding of agonists and antagonists in the solubilized receptor preparations are similar to those measured indirectly from pharmacological dose response curves in the intact electroplax, that is to say, that the receptor sites have not undergone any fundamental change in their properties during the extraction procedure. Changeux and his colleagues also report preliminary results on the use of venom toxins in a new way for the purification of the receptor molecules. The *Naja* α -toxin was used as an affinity chromatography material, by attaching the toxin to an insoluble 'Sephadex' matrix. This material was then used successfully to separate the receptor molecules from acetylcholinesterase in solubilized electroplax preparations. No doubt further purification will be reported.

Changeux *et al.* also point out that the total number of receptor sites determined in their studies in electroplax preparations correspond fairly closely to the number of "receptor proteolipid" molecules reported recently from the same preparations by De Robertis and his colleagues (La Torre *et al.*, *Proc. US Nat. Acad. Sci.*, **65**, 716; 1970; De Robertis *et al.*, *Mol. Pharmacol.*, **7**, 97; 1970). These workers have used a completely different method for extracting a proteolipid fraction which has cholinergic receptor sites, as judged by its ability to bind radioactively labelled hexamethonium at curaresensitive sites.

This sudden flourishing of molecular pharmacology seems to show no signs of abatement; each month now brings some new instalment.

CHROMATIN

Histone History

from our Molecular Biology Correspondent
Most workers in the field would probably agree that the state of knowledge about chromatin structure is one of the disappointments of molecular biology. In spite of prodigious efforts, the amount of hard information is dispiritingly small, and inadequate and contradictory results, not to say artefacts, have over the years been left lying like banana skins in the literature. The fact is that the system has turned out to be

much more refractory than might have been hoped, and such successes as there have been have largely devolved upon the structure and properties of isolated components, such as the histones, the chemistry of which has recently been considerably clarified. In particular, the number of components is now known to be much smaller than was at one time supposed, and some of them have been meticulously characterized and even sequenced.

A feature of several of the histones is evidently a compositional polarization, one end of the molecule being strongly basic, the other preponderantly hydrophobic. This pattern must be expected to govern the conformation of the chain as well as its interaction with DNA. Recently, for example, Bradbury and his colleagues (*Nature New Biology*, **233**, 265; 1971) examined the separated halves of histone F2b, which by good fortune can be obtained by chemical cleavage at the two methionine residues, lying close together in the middle of the chain. The histone, it must be understood, is no globular protein, but rather a flexible chain which will change its structure in response to ionic strength, pH or temperature. The amino-terminal half contains most of the basic residues, and remains (as judged by optical rotatory dispersion) a random coil irrespective of ionic strength, and only by 2 M sodium chloride does aggregation set in. The other half by contrast becomes progressively more α -helical as the ionic strength increases. Proton

magnetic resonance spectra indicate where, in the sequences of both halves, partial conformational freezing occurs, and it is the two regions (one at either end of the chain) which remain mobile and unaffected by salt that, on the evidence of earlier work, preferentially stick to DNA. This is consistent with the view of the histone as a glue which draws parts of a DNA chain together.

A similar picture emerges from the observations of Fasman, Valenzuela and Adler (*Biochemistry*, **10**, 3795; 1971) on the lysine-rich F-1 histone. This again has a polarized sequence, and can be chemically broken at a tyrosine into fragments of 6,000 and 15,000, the second containing the bulk of the lysines and also the prolines. Now when basic polymers are added in high molar ratios to DNA, a striking, though improperly understood, phenomenon is often observed, involving the inversion and magnification of optical activity of the DNA. Such an effect is encompassed by intact F-1 histone, and by the basic C-terminal piece, but not by the N-terminal fragment, though this too binds to the DNA. With both fragments together, the effect is enhanced to a level greater than that produced by the intact chain. The inference is that the C-terminal end is the structurally important DNA-binding site, and that the N-terminal part serves a modifying or cross-linking function.

The self-association of histones has also been advanced as a clue in determining chromatin structure, and it is

Embryonal Antigens and Human Carcinomas

OVER the past several years a great body of evidence has been accumulated, indicating that the cells of malignant tumours, and cells transformed by carcinogens *in vitro*, carry antigens which are not found in normal adult tissues but can be detected in embryonic tissue. Last year, for example, Stonehill and Bendich (*Nature*, **228**, 370; 1970), working with mice, reported detecting embryonal antigens in a wide variety of carcinomas of adult mice and now Klavins, Mesa-Tejada and Weiss, as they report in next week's *Nature New Biology*, claim that "immunologically definable embryonic cell components are universally present in human carcinomas".

Klavins *et al.* raised anti-human embryonic antibody by repeatedly immunizing a rabbit with Freund's adjuvant and a lyophilized extract made from a 6-7 week old human foetus from an ectopic pregnancy. The serum from the rabbit was first absorbed against extracts from normal, adult, human heart, lung, spleen, kidney and intestinal tissue and was then tested by the

Ouchterlony double-diffusion technique against extracts from a variety of human carcinomas including lung, breast and colon carcinomas.

The antifoetal antiserum cross reacted with all six sorts of carcinoma extracts, with extracts of normal, adult, human skin but not with extracts from corresponding normal adult tissues. In short, human carcinomas, but not normal adult tissues apart from the skin, carry antigens which cross react with anti-foetal antisera. As Klavins *et al.* point out, such cross reactions do not prove that the foetal and carcinoma cells carry chemically identical antigens; but the fact that extracts of tumours and embryonic tissues behave identically on 'Sephadex G-200', as well as cross reacting in the Ouchterlony test, strongly suggests chemical as well as immunological identity. The mechanism by which embryonic antigens are caused to reappear after transformation to malignancy, and the exploitation of this phenomenon in diagnosis and perhaps therapy of cancer, will no doubt receive the attention they deserve.

known that some histones aggregate extensively in dilute salt solutions. Diggle and Peacocke (*FEBS Lett.*, **18**, 138; 1971) have shown, by osmometry and sedimentation equilibrium, that one species (F2c) does not aggregate at all, that three others (F2b, F2a2 and F3) aggregated in varying degree, and that F2a1 forms very large and apparently monodisperse aggregates. The results are in good accord, where comparison is possible, with inferences from PMR spectra.

In the altogether murkier area of whole chromatin, Itzhaki (*Biochem. J.*, **125**, 221; 1971) has drawn some conclusions from deoxyribonuclease digestion experiments. With two different nucleases, a considerable part of the DNA is hydrolysed, and appreciable amounts of protein, it is reported, are released with the soluble nucleotide material. The interpretation is that, since proteins fall off during the digestion, no very large tracts of DNA are completely bare. At some points these results are at odds with the findings of Clark and Felsenfeld, who found less (50 per cent as against 75 per cent) digestible DNA, without release of proteins. The displacement or migration of proteins is a hazard in this approach.

Clark and Felsenfeld accordingly performed their digestions under conditions in which they showed that the protein binding was not labile, and also when protein had been covalently attached to the DNA by prior chemical treatment. The reasons for the discrepancy are not therefore obvious. It may turn out to hinge on differences in the preparations, and on the properties of the urea-containing solvent used by Itzhaki, which, it is supposed, solubilizes free protein but not DNA-protein complexes. An interesting feature of Itzhaki's results is that in the presence of moderate magnesium concentrations chromatin is more rapidly digested than free DNA.

Just how careful one has to be in interpreting any results based on the interaction of enzymes with chromatin is the message that emerges from a paper by Hoare and Johns (*Biochim. Biophys. Acta*, **247**, 108; 1971). They measure the template activity of complexes of DNA with each of the main histone fractions as a function of the ratio of DNA to histone. Each fraction progressively inhibits the activity, and does so in a manner almost precisely paralleling the fractional precipitation of DNA. Because the same workers also showed that when the complex is solubilized by a large excess of histone (which moves it away from the charge equivalence region), the template activity is regained, it seems that this activity is substantially determined by the physical state of the material. The histone is evidently not capable in itself of blocking access to the polymerase.

NEONATES

Jaundice and the Pill

from a Correspondent

THE introduction of oral contraceptives in Britain in 1960 followed three years later by reports of breast milk as a cause of jaundice in young babies may be more than just coincidental. Oestriol—a derivative of oestrogen—when given to newborn babies is known to increase the level of bilirubin in the blood, making the infant jaundiced, and it has been suspected from *in vitro* studies that pregnanediol—a breakdown product of progesterone—is a factor which prevents the excretion of bilirubin (in fact, it inhibits the enzyme glucuronyl transferase which conjugates the bilirubin,

making it water soluble and easily excreted by the kidneys). Almost all oral contraceptives are, of course, a combination of oestrogen and progesterone. But these hormones in the pill had not been considered as a factor in causing jaundice in babies because of the interval between the mother ceasing to take the pill and the birth of her baby.

It seems, however, from an article by Y. K. Wong and B. S. B. Wood of Birmingham Maternity Hospital, that the contraceptive pill and jaundice in the newborn may in fact be linked (*Brit. Med. J.*, **4**, 403; 1971). They report a prospective study of infants in the first few days of life who developed jaundice that was not attributable to any of the well-documented causes such as rhesus factor or prematurity.

Gaseous Diffusion in Homologous Series

REGULAR behaviour or systematic change in an observable property as a homologous series is traversed is always a welcome feature of an investigation, not merely because a regularity which is closely adhered to is a flattering reflexion of a carefully conducted set of experiments, but also because such a trend, particularly when linear, may sometimes be used for making predictions.

It is not really surprising to discover that the diffusion coefficients for the gaseous transport of a range of members of a homologous series through a common gas depend on the carbon number of the diffusing molecule. Some dependence would be expected, even on the basis of elementary diffusion theory, because the transport rate is a function of molecular velocity which is a function of molecular mass. What is surprising is that the dependence reported by Elliott and Watts in next week's *Nature Physical Science* is of such a simple linear form, namely

$$D = A\mu + B$$

where D is the diffusion coefficient of a member of the series into a common gas and μ is the reduced mass defined by $\mu = M_H M_G / (M_H + M_G)$ M_H and M_G being the molecular weights of the homologous series gas and the common gas respectively.

Elliott and Watts have observed this relationship for the diffusion into air of a series of normal alkanes (paper presented at the twenty-seventh annual fall scientific meeting, Midland Section, American Chemical Society, October 24, 1970, and to be published in the *Canadian Journal of Chemistry*), but point out that results published in 1963 by Seager, Geertson and Giddings (*J. Chem. Eng. Data*, **8**, 168; 1963) also conform. In their latest communication Elliott and Watts only present

results for the experiments of Seager *et al.*, but these, and also apparently those of Elliott and Watts, show that plots of D against μ are accurately linear (D decreasing with increasing μ) and that the intercept on the μ axis is close to the molecular weight of the common gas (for example, intercept 4.087 to 4.103 for He as common gas).

The predictive uses of this sort of simple linear relationship, particularly if it proves to be generally applicable to many different homologous series, are obvious. It seems likely that the applicability will be general because the series in the two systems described—normal alkanes (in air) and normal alkyl alcohols (in helium)—differ considerably in polarity. It is not clear, however, whether the relationship is still valid if the common gas has considerable polarity. Until the Elliott and Watts conference paper is published it is also not possible to decide to what extent the trend is primarily a mass effect and to what extent molecular shape and size play a part; this point could be checked by examining the diffusion coefficients of isomers of particular members of a series.

The theoretical interpretations of these observations are not clear, although the treatment of diffusion in binary systems in terms of realistic models is far from settled. The use of the reduced molecular weight is common practice when discussing diffusion in binary systems, but many of the published treatments (see Jost, *Diffusion in Solids, Liquid and Gases*, Academic Press; 1952) relate the diffusion coefficient to the reciprocal of the square root of μ ; collision diameter is, of course, also an important factor in all existing treatments. It will be interesting to see to what extent Elliott and Watts have attempted to explain their observations in terms of existing models.

In an investigation of 116 mothers and their breast-fed infants, there was no correlation between jaundice and birth weight, gestation, sex, birth rank or age of mother. But, as Wong and Wood say, "Of the 69 non-jaundiced infants 24 (34.8%) mothers had been on the pill; of the 47 jaundiced infants 33 (70.2%) mothers had been on the pill." Fifty-seven mothers in the study had been on the pill and 59 had not. There seemed to be no difference in the pattern of pill-taking between those mothers who had taken the pill and whose babies were jaundiced, and those mothers who had taken the pill but whose babies were not jaundiced.

But Wong and Wood seem to be at a loss to account for the link between the increased incidence of jaundice and the pill; pregnanediol, for example, is always present in breast milk, but it is hard to see how its effect could be enhanced by the consumption of the contraceptive pill many months before breast feeding begins. Nevertheless, as Wong and Wood say, the figures speak for themselves, and will attract much attention among obstetricians and paediatricians.

FISH

Surgeon Fish's Scalpels

from our Marine Vertebrate Correspondent

SURGEON fishes are widely distributed herbivorous fishes of shallow tropical seas. Many species are known of these mostly colourful fishes and all possess a basic deep-bodied but laterally compressed form. Their common name is derived from a sharp scalpel-like spine placed either side of the body just in front of the tail fin; the spines resemble the surgeon's scalpel in both shape and acuity. These spines (members of four of the recognized genera have one each side; others have two or more) are attached posteriorly with the free sharp point projecting forwards, although the whole spine slots neatly into a groove in the side.

It seems axiomatic that fishes possessing such formidable armament should be able to use it in everyday life, and this aspect of the biology of the surgeon fish has recently been commented on by R. Winterbottom (*Copeia*, No. 3, 562; 1971). Winterbottom reviews earlier studies on the musculature of the spines. Although the presence of four superficial muscles attaching to the base of the spine had been described originally, later workers have been unable either to detect them or to prove an attachment to the spine. Dissection shows that apart from some connective tissue between the spine base and the superficial musculature the only important connexion is ligamentary between the spine and the posterior vertebrae. How then does the surgeon fish erect its spines for use?

Having studied the behaviour of living specimens in an aquarium when presented with a mirror, Winterbottom found that a strong response was evoked in the fish, which changed colour and raised its fins. More significantly, the fish would swim in a tight circle lashing its tail strongly as it passed the mirror. It also rested close to the mirror with body flexed and beat at its image with its tail. Winterbottom concludes from this and from handling the living fish that the spines are not muscularly controlled, but that they are partially erected by the bending of the tail as the body flexes. Thus when swimming strongly to escape, or in attacks on an intruder, the spines would be alternately exposed with each beat of the tail, and contact with them while the fish was moving forward would cause the erection of the whole spine into its fully exposed position as well as driving it into the adversary.

Several cases of wounds caused by surgeon fish in man have been recorded, some of them to persons carelessly handling live fish which presumably wagged their tails in escape movements driving their spines into their captor's hand. Several surgeon fishes appear to have envenomed spines and wounds from these species can be extremely painful. Even lacking an erecting musculature it is obvious that the surgeon fish's spines are more than adequate defensive weapons.

A Direct Acting Colicin

THE way in which that most curious class of proteins, the colicins, which are specified by extrachromosomal genes, are able to kill susceptible *E. coli* cells but do not kill their own host cells has long puzzled bacteriologists. In *Nature New Biology* next week, Nomura's group, adding another chapter to their most elegant exposition of the biology of colicin E3, explain how host cells develop specific immunity to this colicin and report evidence which suggests that the colicin penetrates susceptible cells and itself attacks their ribosomes.

Colicin E3 is, as Nomura and his colleagues and others have shown, a protein which kills *E. coli* by inactivating their 30S ribosomal subunits. The colicin causes a fragment of about 50 bases long to be cleaved from the 3' end of the 16S RNA in the 30S ribosomal subunits. Until recently, most researchers who have worked with E3 and other colicins, which kill cells in quite unrelated ways, have suggested that these proteins remain on the surface of the cells to which they adsorb and mediate their lethal effect by causing some membrane change, rather than by entering the cell. This hypothesis now seems untenable as far as colicin E3 is concerned. Bowman, Sidi-

PHOTOCHEMISTRY

Nonlinear Photolysis

from our Molecular Physics Correspondent

AN important, though not unexpected, advance in photochemistry has been taken with the demonstration of what appears to be the first clear-cut two-photon decomposition reaction in the gas phase. S. Speiser, I. Oref, T. Goldstein and S. Kimel of Technion, Israel Institute of Technology, now seem to have proved beyond reasonable doubt that the photolysis of azoethane ($C_2H_5NNC_2H_5$) observed when it is irradiated at very high intensity at a wavelength to which it is nominally "transparent" can only be due to the simultaneous absorption of two quanta of the available light (*Chem. Phys. Lett.*, 11, 117; 1971).

The normal, well-studied photolysis of azoethane takes place with light at a wavelength of around 352 nm with a quantum yield of some 0.8. Speiser and coworkers selected the convenient ruby laser frequency of 694.3 nm and by means of a Q-switching arrangement were able to administer a series of pulses of extremely high energy in this region where normally nothing would be expected to occur. They duly observed the liberation of nitrogen and were able to show that its production was very nearly proportional to the square of the pulse intensity, indicating

karo and Nomura have proved beyond doubt that *in vitro*, in the complete absence of any membrane, pure colicin E3 protein cleaves the 3' end of 16S RNA in 30S ribosomes at the same point at which the 16S RNA is cleaved *in vivo*. In other words, the colicin attacks its target, the 30S ribosome, directly *in vitro*.

And that is not all. Bowman *et al.* have discovered that cells which carry the colicin E3 genetic factor and make E3 protein contain a substance or substances which protect the colicinogenic cell's ribosomes from attack by the colicin. In other words, cells which make colicin E3 are able to survive because they make an antagonist to E3. Presumably, past failures to detect *in vitro* the activity of colicin E3 reflect the fact that the impure preparations of colicin used contained this protective substance(s).

The fact that colicin E3 can act directly *in vitro* strongly suggests that *in vivo* it penetrates susceptible cells and directly attacks their ribosomes, rather than causing some change in the cell surface which in turn inactivates the ribosomes. If this is true of colicin E3, then it may well be true of other colicins.

that photolysis was occurring with the absorption of two quanta, as though at an effective wavelength of 347 nm. The two-photon reaction cross-section proved to be $6.5 \pm 2.5 \times 10^{-52}$ cm⁴ s/photon mole, probably the first measurement of its kind.

Two-photon effects have been demonstrated before in solution reactions (for example, see S. Speiser and S. Kimel, *J. Chem. Phys.*, **51**, 5614; 1969), although in these the unpleasant complication of solvent effects is worsened by the strange phenomenon of self-focusing in the laser beam. This occurs when the light intensity becomes so great as to modify the refractive index of the liquid and cause a lens-like focusing towards the beam axis. Although this, if anything, increases the tendency to two-photon reaction, it complicates considerably the calculation of effective cross-sections, because the true intensity profile must be estimated through the nonlinear optics involved.

Although a satisfactory theory of multi-photon rate processes may be some time in arriving, it is perhaps not too soon to ponder some of the problems which are raised by the existence of such processes. The first will not worry anyone unduly, although it is amusing: where ultra-high intensities are involved one must now exercise some caution in referring to a substance as "transparent" to a certain wavelength so long as an absorption band is present higher up the energy-scale. Second, and more serious, it is perhaps time to ask whether quite new photochemical influences may be at work under these conditions where the magnitudes of electric and magnetic field vectors in the neighbourhood of the molecules become so enormous. Any peculiarities which may emerge as the theory of dielectrics at extreme fields develops may well prove to have chemical effects not simply connected to the transition probabilities for photon absorption.

PLANT ENZYMES

Coordinate Induction?

from our Phytochemistry Correspondent

SUBSTRATE induction of enzymes (that is, their synthesis in response to the presence of their substrates) is now commonplace in microorganisms and not infrequent in higher animals. In higher plants, however, substrate induction is a rare phenomenon and it is therefore gratifying to see significant progress being made towards the full understanding of the one well authenticated example, the induction by nitrate of the nitrate assimilation system. The latest advance in this campaign is the demonstration by Kelker and Filner (*Biochim. Biophys. Acta*, **252**, 69; 1971) that nitrate induces both nitrate and nitrite reductase in a simultaneous rather than a sequential manner. It has been known for several years that the application of nitrate to plants previously grown on nitrate-free medium led in many cases to the appearance of high levels of nitrate reductase and nitrite reductase, the enzymes which catalyse the first two reactions in the reductive assimilation of nitrate. In 1966 Ingle, Joy and Hageman (*Biochem. J.*, **100**, 577; 1966) reported a three-hour lag between the induction of nitrate reductase and that of nitrite reductase in radish cotyledons and proposed that the rise in nitrite reductase activity was dependent on the

prior formation of nitrite by the action of newly formed nitrate reductase. In other reports, however, identical time-courses for the appearance of the two enzymes in response to nitrate were found, supporting a simultaneous rather than a sequential induction mechanism.

To test this question critically, use was made of the knowledge that tungstate inhibits the development of nitrate reductase (a molybdo-protein), probably by being incorporated in place of molybdenum, thus forming a non-functional enzyme (Wray and Filner, *Biochem. J.*, **119**, 715; 1970). Using exponentially growing tobacco cells in suspension culture, Kelker and Filner showed that transference from a nitrate-free medium to a medium containing both nitrate and tungstate led to normal appearance of nitrite reductase in the absence of any increase in nitrate reductase activity. In these conditions, added nitrate could not be converted *in vivo* into nitrite and the authors logically conclude that nitrate directly induces nitrite reductase. Earlier this year, the same group provided evidence that nitrate induces the formation of the nitrate-uptake system in tobacco cells (Heimer and Filner, *Biochim. Biophys. Acta*, **230**, 362; 1971) while in barley shoots nitrate also induces an NADH-cytochrome *c* reductase (Wray and Filner, *ibid.*).

It seems clear, therefore, that the development of several biochemical activities intimately involved in the

Genes to Switch off Host

WHEN bacteriophages such as P22, λ , or the T even phages infect bacteria the overall RNA and protein synthesis of the infected cell is either transiently or permanently depressed. Where a lysogenic phage such as P22 is involved this depression of the host's macromolecular metabolism is permanent if the infection leads to cell lysis, but transient if it leads to lysogeny. The possible role of phage genes in these changes has been widely debated for many years and in next Wednesday's *Nature New Biology* Chakravorty and Bhattacharya of the Banaras Hindu University report experiments which clearly implicate genes of phage P22 in the inhibition of RNA and protein synthesis in *Salmonella typhimurium*.

Exploiting mutant as well as wild type phage, Chakravorty and Bhattacharya established that the extent of inhibition of RNA and protein synthesis depends on the multiplicity of infection and also that RNA and protein synthesis can be independently depressed. They then measured the depression of macromolecular synthesis when *S. typhimurium* cells, lysogenized either by wild type P22, which has an intact *sie*⁺ gene and specifies an active *sie* protein, or by

mutant *sie*⁻ phage, are superinfected with wild type P22. The RNA and protein synthesis of lysogens carrying the mutated *sie*⁻ gene is transiently depressed on superinfection. By contrast, superinfection with P22 does not depress the metabolism of *sie*⁺ lysogens. In other words, cells which carry a *sie*⁺ gene and make active *sie* protein—which may well be analogous to the *C* gene repressor protein of phage λ —do not suffer transient depression of their macromolecular synthesis on superinfection, because the *sie*⁺ protein prevents expression of any of the genes of the superinfecting phages, including those which somehow interfere with host metabolism. Experiments with a mutant of P22, which is virulent probably because it does not respond to the *sie* gene repressor, support this argument. Superinfection of a *sie*⁺ lysogen with the virulent mutant P22 results in a transient depression of RNA synthesis.

In summary then, the depression of cellular RNA and protein synthesis following infection with P22 appears to depend on the expression of some P22 genes, which is probably regulated by the product of the *sie* gene.

ZOOLOGY

New NERC Unit

THE Insect Pathology Unit (under Dr T. W. Tinsley) at the University of Oxford, which has been supported for the past five years by a grant in aid from the Natural Environment Research Council, has now been brought directly under the council with the title of Unit of Invertebrate Virology and with Dr Tinsley as director. The unit will carry out basic studies on the viruses and viral diseases of invertebrates.

assimilation of nitrate by higher plants is regulated by nitrate in a manner which, at least superficially, resembles the coordinate regulation of the *lac* operon in *E. coli*. Although it would be dangerous to conclude from this that similar mechanisms are at work in *E. coli* and tobacco cells, it is nevertheless cause for some celebration whenever the plant kingdom is brought one step nearer the molecular empire. It is to be hoped that further probing of the nitrate assimilation system will lead to discoveries of importance for our understanding of the regulation of gene expression, not only in plants, but also in other eukaryotes.

REVERSE TRANSCRIPTASE

Enzyme with Many Uses

from our Cell Biology Correspondent

A SUPPLY of radioactively labelled DNA molecules complementary to either messenger RNAs or the genomic RNAs of the RNA viruses is something molecular hybridizers have long dreamed of; as specific probes, such DNA molecules would be invaluable when it comes to detecting, for example, the location of genes on chromosomes, the sites of replication of RNA viruses or specific RNAs or DNAs in complex mixtures. The discovery of reverse transcriptase raised hopes that such DNAs might become available; everything depended on the degree to which this enzyme in RNA tumour virus particles is template specific. If reverse transcriptase shared the rigid template specificity shown by phage Q β RNA replicase—an enzyme which can only use Q β RNA and variant molecules derived from it—its use would be very restricted, but what if tumour virus reverse transcriptase proved to lack substantial template specificity? This enzyme could then be used to make a DNA complementary to all sorts of RNAs. In the event, as Spiegelman, Watson and Kacian report (*Proc. US Nat. Acad. Sci.*, **68**, 2843; 1971), the reverse transcriptase isolatable from avian myeloblastosis virus particles (AMV is readily available in large quantities, unlike many other RNA tumour viruses) seems to lack rigorous template specificity.

This enzyme, which when pure has been shown to consist of equimolar amounts of two polypeptide chains weighing 110,000 and 69,000 daltons (Kacian *et al.*, *Biochim. Biophys. Acta*, **246**, 365; 1971), will reverse transcribe, albeit at different efficiencies, not only AMV RNA and synthetic homopolymer duplexes but also natural RNAs from sources as diverse as Q β phage and Moloney mouse sarcoma virus. In short, reverse transcriptase lacking template specificity should prove to be an enormously useful enzyme.

And if the experiments of Crippa and Tocchini-Valentini (*Proc. US Nat. Acad. Sci.*, **68**, 2769; 1971) and Ficq and Brachet (*ibid.*, 2774) are anything to judge by, it seems that an RNA dependent DNA polymerase (reverse transcriptase) may exist in eukaryotes and play a crucial part in processes such as gene amplification. During oogenesis in the toad *Xenopus laevis* genes specifying ribosomal RNA, which, including a spacer DNA, form a unit about 9×10^6 daltons, are amplified. Crippa and Tocchini-Valentini have attempted to implicate a reverse transcriptase in this process. They have shown, using 5-bromodeoxyuridine as a density label, that the ribosomal DNA cistrons are not themselves apparently used as a template for their own amplification. This finding suggests, of course, that the template for the amplification of the ribosomal DNA cistrons

may be an RNA rather than a DNA.

Crippa and Tocchini-Valentini have also shown that, albeit at fairly high concentrations, 2',5'-dimethyl-N(4')benzyl-N(4')[desmethyl]rifampicin, a drug which is known to inhibit the activity of reverse transcriptase in tumour viruses (Gurgo *et al.*, *Nature New Biology*, **229**, 111; 1971), inhibits gene amplification during oogenesis in *Xenopus*. This, of course, suggests that the enzyme responsible for amplifying these genes may be a reverse transcriptase. Ficq and Brachet, using autoradiography to monitor the amplification of ribosomal DNA in *Xenopus* oocytes, also show that this drug inhibits the process and draw the same conclusion. It may well be therefore that ribosomal DNA amplification depends on the transcription of the ribosomal DNA cistron into a 47S RNA transcript which is then used as a template by reverse transcriptase.

Laser Studies of Vibrational Energy States

THE availability of high-powered monochromatic beams of laser light, which are well collimated and usually polarized, together with the fact that they may be modulated or pulsed in times as short as 10^{-11} s, has promoted research into many new areas in the field of electromagnetic/vibrational energy interaction.

Energy distribution among the various vibrational modes of single molecules and the interchange of vibrational energy between molecules following laser excitation have become fruitful areas of investigation in recent years. Selection of a laser wavelength which exactly matches an absorption line in a molecule makes it possible to populate efficiently a single vibrational energy state. At present more than twenty vibrational bands, exactly matched by laser frequencies, are known. The rates of the various vibrational energy transfer processes which follow the absorption may be determined with comparative ease and this fact, together with the rapidly expanding number of systems which are becoming amenable to experiment, has made both practical and theoretical approaches profitable.

Since the simultaneous appearance in the literature of the first two reports of laser excited vibrational (infrared) fluorescence, the first involving the asymmetric stretching mode (001) of carbon dioxide and the second involving the bending mode of methane, laser excited vibrational fluorescence experiments have considerably increased the detailed understanding in this field. Several kinds of chemical lasers have been described. Typically, infrared fluorescence originates from rotational lines in the vibrational spectrum of HCl which is formed by flash photolysis of

fast flowing mixtures of chlorine and hydrogen. In HCl-CO₂ mixtures both HCl and CO₂ fluorescence have been observed.

In the closely related techniques of double resonance which may involve infrared, microwave or a combination of both kinds of radiation, changes in the vibrational-rotational energy distribution produced by the absorption of a pulse are monitored by means of absorption changes. In the presence of strong monochromatic resonant radiation molecules no longer assume a Boltzmann distribution. If the radiation is applied continuously a steady state will be produced in which the population of a particular level n_i is different from that for a Boltzmann distribution n_i^0 . The value of $n_i - n_i^0$ depends on the power of the radiation and the relaxation time between the levels. Double resonance techniques enable the values of $(n_i - n_i^0) - (n_j - n_j^0)$ to be measured and therefore provide a powerful insight into the mechanisms of relaxation processes. Collisional relaxation of the (100) state of CO₂ itself has been studied by this technique using CO₂ lasers as pumping and monitoring sources while the more general applicability of the method has been demonstrated in a study of the relaxation processes in SF₆.

As well as the energy transfer studies already mentioned, some uncertainty about the initial absorption process still remains, particularly in cases where the high photon density of the laser beam brings about the involvement of multi-quantum processes. In particular, the communication by R. T. Bailey, F. R. Cruickshank and T. R. Jones in next Monday's *Nature Physical Science* should help to resolve some problems.

SURVEY OF NORTH AMERICAN SCIENCE

Signs of Change in Science Policy

IN the past few months, Washington's science policy machinery has been working overtime on plans that could significantly alter relationships between science and government in the United States. The result of all this work is likely to be a change of direction in American science policy rather than a wholesale increase in the total research and development budget, and although industrial technology will probably be the chief beneficiary, the universities are also likely to feel some eddies from the winds of change that are swirling around the White House.

What is going on in the scientific bureaucracy is no less than an attempt to redirect and stimulate research and development along lines that will help to solve economic and social problems—in essence another form of the white-hot technological revolution hailed by Mr Harold Wilson as the answer to Britain's economic problems in the early 1960s. Four chief factors have combined to stimulate the Administration's interest in science and technology: unemployment, which among scientists and engineers is running at its highest level since the war, the flagging domestic economy, the trade deficit and the especially bad trading figures for high technology products. But perhaps the chief factor in the drive to find new ways to put science and technology to better social use is the desire to inject new life into the economy and reduce the numbers of unemployed in time for next year's Presidential election.

The ideas that are now being discussed in the White House will, however, have an impact that is likely to outlast any temporary pre-election boom, for they call for a rather fundamental change in the relationship between government and industry on all kinds of research and development. In short, what is happening is that some members of the White House staff are busily engaged in sifting through a list of scientific projects submitted by industry and by government agencies, and it is hoped that a package will be put together in time for next year's budget message so that President Nixon can announce that the Administration is backing a range of socially-orientated technological projects. The backing is likely to take the form of tax incentives or even subsidies which will make the government a partner in all kinds of industrial research. Another part of the package may be a relaxation in the anti-trust laws to allow companies in the United States to get together on research and development in areas such as pollution control.

Such ideas are not new—they have been canvassed in various government departments for years—but until recently there has been little serious attempt to take a firm grip on the problems involved in making a reality out of the political rhetoric that says that science and technology should be brought to bear on social problems. In the heady days of the 1950s and early 1960s, the vague promise that a brave new world would be built from science and technology was sufficient to justify pouring more and more dollars into science's coffers. Before long, however, administrators began to look more closely at the relationship between research and economic growth, and the budgetary emphasis was placed on those technolo-

gies likely to have some payoff for national well-being. The latest moves in the Administration are effectively aimed at first determining the problems and then looking around not only for new technologies that may help to solve them but also for ways to adapt old technologies in new ways.

The Office of Science and Technology began almost a year ago to look around for such new "technological initiatives", but the project did not really begin to take on a definite shape until this summer, when two senior members of the Administration—Maurice Stans, Secretary of Commerce, and Murray L. Weidenbaum, Assistant Secretary of the Treasury—hinted in testimony to a Congressional committee that something strange was afoot in the upper echelons of the science bureaucracy. Stans suggested that some method should be found for stimulating civilian research and development because the level of investment in this sector during the past few years has been stagnant. The upshot, he suggested, has been that the United States is sitting on the sidelines watching other countries grow and prosper and that it is about time that serious consideration was given to such devices as loan guarantees, cost sharing, grants and procurement incentives for stimulating industrial research and development. Weidenbaum maintained that "there are strong indications that as a nation we may now become too niggardly in our overall support of science, engineering and the related intellectual activities that are so fundamental to our growth and progress". His chief suggestion was that the government should consider tinkering with the tax structure to provide some incentive for firms to offset the risks involved in embarking on technological projects.

In September, all these various trains of thought were brought one step nearer realization when William M. Magruder, the Administration's champion of the ill-fated SST, was appointed to the White House staff with the title of special consultant to the President on links between research and development and high technology exports. His appointment, made without fanfare, caused barely a ripple in the White House watcher corps, until it became obvious that his brief is much wider than his title suggests. He is, in short, the man who has been charged with the task of coordinating and expanding the "technology initiatives" project started by the Office of Science and Technology, and with stimulating civilian research and development.

Magruder's appointment is widely viewed, at least out-

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side immediate White House circles, as a slap in the face for the Office of Science and Technology, for he has effectively taken over the chief responsibility for one of the OST's most important programmes; there has been no shortage of speculation that his appointment marks a downward shift in the influence of Edward E. David Jr., the President's Science Adviser and head of the OST.

The OST staff in fact reacted to the appointment with some misgivings, but they are now saying that Magruder is more an ally than a threat to their influence, because the OST is in any case not properly equipped for dealing with such a highly political issue. David himself says that Magruder's appointment has not affected the status of the OST, and that his own relations with the President have not been changed at all. There is no denying, however, that the "technological initiatives" programme is an important area of policy in which the OST has already invested considerable time. Indeed, the outcome of the project is likely to determine many facets of the Administration's links with science, and therefore the relegation of David to a secondary role does not augur well for the OST or for the influence of academic scientists.

What effect the Administration's newfound interest in research and development is likely to have on the overall scientific effort is open to question, but there seem at present to be few prospects of a bonanza for basic research in the budget that is now being put together in the White House. The way that budgetary restrictions have already bitten into academic research in the United States can be seen in several institutions like the Princeton-Pennsylvania accelerator which is limping along on private funds because the Atomic Energy Commission's budget could not accommodate it along with the increased funding for the National Accelerator Laboratory at Batavia. In many respects, the decision to deprive the Princeton-Penn accelerator of federal money is symbolic of the fact that the halcyon days of academic research, in which money was made available for all types of project on the slightest justification, are finally at an end.

In 1968, total government expenditure on research and development started on a decline that was only halted in the Administration's budget for the present financial year. Even the 7.6 per cent increase in expenditure asked for in that budget was, however, insufficient to offset the inflation over the past few years, and there were still warning signs that scientists must justify their requests for federal money as rigorously as any other group. To be sure, much of the decline in the science budget could be put down to a slackening in the space programme as the Apollo series nears its end, but the very real signs of financial stringency in the universities bear witness to the fact that budgetary restrictions are biting deep.

The state of high energy physics, apart from the financial situation of the Princeton accelerator, is a good example of how funding policies have changed. The problem here is that the National Accelerator Laboratory is soaking up an increasing share of the funding for higher energy physics, and other enterprises are being cut out as a result. In the not too distant past, the total high energy physics budget might have grown to accommodate the increasing cost of the National Accelerator Laboratory, but the weaker laboratories now have their backs firmly to the wall. The Joint Committee on Atomic Energy, in its report on the authorizations for the Atomic Energy Commission this year, in fact warned that the trend of declin-

ing high energy physics funds must be sharply reversed if all existing laboratories are to be kept open, and asked the AEC for a priority listing of which establishments should be kept open if budgets continue to decline.

Radio astronomy is yet another area where insufficient funding has caused undue belt tightening. Three years ago a panel under the direction of Professor R. H. Dicke of Princeton University drew up a list of projects on which the Federal government could usefully make a start but, so far, the only suggestion taken up is that a new surface should be provided for the Arecibo telescope. Another review of the standing of astronomy has, however, just been completed by a panel under the direction of Professor Jesse Greenstein of California Institute of Technology, and it seems that radio astronomy may get a long overdue injection of funds in the coming budget.

Another field of research that can face the future with confidence—at least as far as funding is concerned—is cancer research in particular and health research in general. The tussle over the organization of cancer research that has occupied two congressional committees and many lobbyists on Capitol Hill during the past year has been remarkable not so much for the ideas that have been put forward, but for the fact that it has been almost taken for granted that, however cancer research is finally administered, it will enjoy a massive budget. The Administration's stake in the enterprise has already been demonstrated by President Nixon's request for an extra \$100 million for cancer research this year, and by unceasing efforts of the White House to get its name on whatever legislation finally goes through Congress.

The Administration's preoccupation with applied research is also likely to leave its mark on the budget for the National Science Foundation, at least as far as the portion devoted to the programme known as Research Applied to National Needs (RANN) is concerned. This year's budget for the NSF in fact represents an increase of some 22 per cent compared with the money the foundation spent last year, the chief increase being for funds devoted to picking up projects shed by other agencies, such as the materials research laboratories transferred by ARPA. But the budget that finally emerged from the Congressional mill was very different in character from that requested by the Administration.

Congress, in short, applied the knife to some of the projects that the Administration had wanted to stimulate, such as RANN, and added funds to some of the educational programmes, such as institutional and graduate support, that the Administration had wanted to run down. The upshot was that Congress gave the Administration the \$622 million it asked for, but the Office of Management and Budget immediately impounded \$32 million of the extra money voted for educational support as part of "the anti-inflation plan" thereby reducing the foundation's total budget to some \$590 million.

The rationale behind the desire to cut out some of the funding for graduate support is that the pool of unemployed scientists and technologists is already embarrassingly large, and the Administration wants to slow down the rate of production of postgraduates. The whole tug of war is, however, likely to have a second showing next year if the Administration continues on the same tack—and to judge by its recent fascination with applied research and with reducing the numbers of unemployed, a repeat performance is certainly possible.

ASTRONOMY

Twenty-five Years of Rocket and Satellite Astronomy

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On October 10, 1946, a V-2 rocket, instrumented by the Naval Research Laboratory, was launched from White Sands, New Mexico, and carried an ultraviolet spectrograph above the ozone layer to photograph the solar ultraviolet spectrum. After twenty-five years of rocket astronomy, it is therefore appropriate to trace some of the history of astronomy from space platforms.

SUPPORT for space research in astronomy in the United States has been generous and on the whole the scientific returns have been very rewarding. The flow of new information is in the mainstream of the remarkable progress of present day astronomy and promises to influence our understanding of the universe even more profoundly in the future.

The V-2 flight in 1946 enabled R. Tousey and his NRL colleagues to photograph the solar spectrum down to 2200 Å. Similar success quickly followed from the efforts of J. J. Hopfield and H. E. Clearman, jun., of the Applied Physics Laboratory. From these beginnings rocket astronomy moved on to a remarkable series of advances in solar spectroscopy, which eventually mapped the entire spectrum to its X-ray limit and led naturally into the study of celestial objects beyond the solar system. Of great importance to all this solar research was the biaxial pointing control developed at the University of Colorado with support from the Air Force Cambridge Research Laboratory.

Photometer Developments

While the first photographic spectrographs were being flown, my colleagues and I sought to develop narrow band photometers for the ultraviolet and X-ray portions of the spectrum. A set of photon counters sensitive to X-rays (1–8 Å) and the ultraviolet bands 1050 to 1350 Å and 1425 to 1600 Å were flown in 1949. This flight provided quantitative measurements of solar X-rays, the hydrogen Lyman- α line and the Schumann continuum region of the ultraviolet; it also gave a comprehensive picture of solar-terrestrial relationships in the D, E and F-regions of the ionosphere. Encouraged by the success of this simple photometric technique we moved on to the exploration of a wider range of astronomical sources.

The earliest attempt (1955) to measure stellar ultraviolet emission employed wide field of view photon counters on an Aerobee rocket. Above 85 km the Lyman- α sensitive detectors quickly saturated in the intense resonance radiation of the hydrogen geocorona. First, by narrowing the field of view and then by moving on to telescopic mirror collection systems, it was possible to do far ultraviolet photometry of early-type stars. In a typical Aerobee rocket flight (utilizing the free spin and precession to scan the sky) the fluxes of some 200 stars could be measured in several ultraviolet bands. When the NASA astronomy programme was conceived at the beginning

of the last decade, the early rocket results afforded guidance in planning the series of Orbiting Astronomical Observatories (OAO).

Rocket Fuels

Liquid-fueled rockets were satisfactory for preassigned launch schedules to observe the X-ray and ultraviolet emissions of the quiet Sun but could not be kept in the launching tower in a "hold" status to await a transient event such as a solar flare. To explore the flare phenomenon, the NRL group made use of the Rockoon, a combination of the Deacon solid propellant rocket and Skyhook balloon. From the deck of a Naval vessel in the Pacific a Rockoon was floated at 80,000 foot each day for ten consecutive days during the summer of 1956 while we waited for evidence of a flare. When a flare occurred, the rocket was ignited by radio command and climbed above the 100 km level to observe the flare radiation. Clear evidence was obtained of the production of hard X-rays by a solar flare and the penetration of this radiation to the base of D-region (about 60 km).

This exploratory effort was followed by the use of two-stage solid-fueled rockets in the International Geophysical Year (IGY) and the accumulation of evidence of flare X-rays of energy up to 100 keV. The rocket experiments led eventually to the Navy Solrad programme which in 1961 began to monitor solar X-ray variability and which is continuing with Solrad-10, launched in July 1970. For refined spectral detail astronomers have used the NASA Orbiting Solar Observatory programme, which recently placed OSO-7 in orbit. This series has provided high resolution X-ray and ultraviolet spectra, as well as ultraviolet spectroheliograms and X-ray images, and the OSO programme is planned to continue through this decade.

An early clue to the possibility of galactic and extragalactic X-ray astronomy came out of the Rockoon Solar Flare Program in 1956. A scintillation counter covering the energy region 30 to 200 keV showed a background flux that was separable from atmospheric emissions. Aerobees flown in the years from 1957 to 1962 carried detectors which searched unsuccessfully for celestial X-rays but the breakthrough finally came with the discovery by Giacconi, Paolini, Gursky and Rossi in 1962 of X-ray emission from the general direction of the galactic centre. Since that historic date X-ray astronomy has produced a succession of surprising discoveries following one on the other in rapid succession.

Advent of Satellites

At the beginning of the 1960s space research in the United States moved into the satellite era. Rocket astronomy had mapped the full solar spectrum to wavelengths as short as a few Å, recorded the transient X-ray bursts of solar flares, photographed the Sun in Lyman- α and in X-rays, discovered the geocorona and measured the far ultraviolet fluxes of early-type stars. These pioneering observations stimulated the planning of the first generation of astronomical satellites but the value of continuing with rockets, and to a lesser extent balloons, as platforms for space astronomy was clearly established.

Throughout the 1960s rocket astronomy continued to lead the way to new discoveries in the ultraviolet and X-ray regions, and the basic ideas for future orbiting astronomical observatories were shaped on the basis of these discoveries. X-ray and gamma ray astronomy, in particular, have generated such interest that the chief astronomy effort in the NASA programme for this decade will be the High Energy Astronomical Observatory series (HEAO).

Some fifty discrete X-ray sources have been found within the galaxy and perhaps the greatest interest centres on those which exhibit various forms of extreme variability. Although the catalogue of radio pulsars has grown steadily, the list of X-ray pulsars includes only the Crab pulsar with certainty. Bursts of pulsar-like emission have been observed from Cyg XR-1, but their lifetimes seem to be transient. Several periodicities from 73 ms to 290 ms have been reported at different times with flux variations as great as a factor of ten. It is difficult to fit this complex behaviour to existing theoretical models of rotating objects. Only in auroral X-ray phenomena have similar transient pulsation characteristics been observed. Cen X-3 shows no radio pulsation but is almost fully modulated in X-ray emission at a period of about 5 s and exhibits abrupt increases and decreases of a few hundredths of 1 per cent in period during time intervals as short as a minute. Is it a neutron star or a white dwarf near rotational instability? Tentative evidence has recently been obtained by Sadeh from an NRL balloon flight of X-rays from NP 0527 at a period of about 4 s. If true, X-rays are emitted from the fastest and slowest radio pulsars, which presents quite a dilemma for existing theories. Furthermore the X-ray period is 2 per cent longer than the radio period. Could this be a relativity effect?

The list of extragalactic X-ray sources now includes the Magellanic clouds, the quasar 3C 273, Seyfert galaxies NGC 1275 and NGC 4151, the Virgo and Coma clusters, the jet galaxy M-87 and the more typical radio galaxy, Cen A. In each of the peculiar galaxies the X-ray source provides the principal portion of the total radiated power. X-ray astronomy of these objects should provide important clues to the mechanisms of nuclear activity. Where several observations have accumulated in recent years, as for M-87, evidence exists for large flux and spectral variations on a time scale as short as a few months. Is the variable emission associated with a spinning super-massive object ($>10^6 M_{\odot}$), groups of magnetoids of $10^4 M_{\odot}$ in the jet or swarms of millions of pulsar-like objects? Is the intense infrared emission from NGC 1275 directly coupled to the X-ray emission, does the X-ray emission heat a dust shell to produce infrared emission, or does the X-ray flux derive from Compton scattering of relativistic electrons on synchrotron infrared quanta in a compact core of diameter about one light year? More refined spectral data and frequent monitoring from satellites will help to answer these questions.

Diffuse Background

Many rocket and satellite observations have confirmed the existence of a diffuse X-ray background which is highly isotropic above 10 keV. The most restrictive limits on spatial fluctuations were derived from OSO-III data in the 8 to 38 keV range by Schwartz and Peterson. Since the discovery of the diffuse background, there has been speculation about whether the source is the sum of unresolved galaxies or whether it arises throughout intergalactic space.

From the high degree of X-ray isotropy, Wolf and Burbidge have argued that super-clusters of galaxies (about 10^6 galaxies over a region of about 50 Mpc) can be ruled out. If the background is produced by high energy electrons within galaxies, or if it leaks out into the surrounding intergalactic space, a map of the X-ray background should resemble the distribution of galaxies. There is no evidence of such anisotropy in the background X-rays and the observations would therefore seem to exclude super-clusters or the still greater hierarchy of super-super-clusters as the source of X-ray background. It

is, in effect, possible to deny on the basis of isotropy the production of background radiation from the sum total of galaxies unless we resort to evolutionary models in which most of the X-rays come from early epochs when the distribution of galaxies may have been much more homogeneous.

For several years, rocket astronomers in the United States, Canada and Japan have sought to extend the X-ray background spectrum to energies as low as 100 eV. As the results become more refined and reliable, it becomes clear that the spectrum bends upwards below 1 keV. Whether this excess is local or extragalactic is still a controversial question; one interpretation is that the soft X-rays are bremsstrahlung radiation from intergalactic gas at $\sim 10^6$ K and that the density accounts for 97 per cent of the mass of a closed universe.

Clusters of Galaxies

During the past year rocket and satellite observations have been made of the large and distant clusters of galaxies in Coma and Virgo. Each cluster contains thousands of galaxies which presumably radiate X-rays like the Milky Way. NRL rocket observations revealed X-ray fluxes about twenty times as great as would be expected from the individual galaxies, and it was suggested that this excess is produced by hot gas ($T > 8 \times 10^6$ K) within the clusters. More refined measurements of Coma by the UHURU satellite showed the emission to be concentrated near the centre of the cluster. The mass of gas would not exceed about $6 \times 10^{13} M_{\odot}$, or about 3 per cent of the total mass of the cluster, which is insufficient to bind the cluster gravitationally. Therefore, unless the cluster contains a large amount of mass in the form of neutron stars and black holes, its component galaxies should be dispersing.

Gott and Gunn have argued that infall of intergalactic gas ought to fill the cluster to a much higher concentration over a period of 10^9 yr than the limit set by the X-ray observations, if the intergalactic gas density is about 10^{-5} cm^{-3} —the critical value for a closed universe. In effect, the accumulation of no more than $6 \times 10^{13} M_{\odot}$ implies a limit on the intergalactic gaseous medium of less than 10 per cent of the mass of a closed universe, according to their estimates. Thus the first-generation measurements of X-ray background and galactic clusters have raised as many questions as they have answered but any models of closed or open universes, of bound or unbound galaxy clusters, must now confront a great deal of new observational evidence.

Future Space Research

A recent study of priorities for space research by the National Academy of Sciences gave greatest weight among new starts in astronomy to HEAO, and recommended a programme of four launches in this decade. The giant spacecraft will weigh 21,000 pound and will be 30 foot long by 8 foot in diameter; its payload of scientific instruments will weigh about 12,500 pound. High energy astronomy can exploit such large payloads to great advantage in cost effectiveness over rockets or the SAS-class satellites. Whereas SAS-1 could accommodate about 2 foot² of X-ray proportional counter sensitive to a narrow band from about 2 keV to 7 keV, the X-ray survey instrument for HEAO-A will have an area of about 60 foot²; it will cover the wide range from 0.2 keV to 200 keV and will have far greater data handling capacity. The individual millisecond pulses of the Crab pulsar, for example, will be recordable with high signal-to-noise ratio. Yet this instrument will cost less than twice that in SAS-1 and will be only one of seven instruments of comparably advanced power for X-ray, gamma-ray, and cosmic-ray observations included in the total payload of the first HEAO scheduled for 1975.

A vigorous rocket and balloon programme during this decade is not made any the less desirable by HEAO. Balloon astronomy is highly effective for studying variability and 1,000 pound payloads can routinely be raised to 150,000 foot for

10 h of observation. Considerably improved instruments are being developed for rocket astronomy and rockets with an order of magnitude greater payload weight and volume could be made available from military surplus at low cost. The NAS study referred to previously recommended a doubling of rocket and balloon support for astronomy, even at the lowest contemplated budget level.

Trends in Optical Astronomy

As the natural follow-on to the OAO programme, the astronomical community supports the goal of a major optical astronomy facility in space, the large space telescope (LST), for the 1980s. It would have an important impact on cosmology. Today's ground-based telescopes cannot establish the value of the deceleration parameter with sufficient certainty to distinguish between an open and a closed universe. At the very best, it may be possible to measure redshifts and to measure galaxies photometrically to magnitudes 21 to 23 with the largest ground-based telescopes. An LST would help greatly to solve the problems of the size and structure of the universe. With better than 0.1 arc sec resolution (3 m mirror) a limiting magnitude of ~ 29 for stellar photometry is attainable, about a hundred times fainter than the ground-based limit. This capability should indicate the cosmological scale and curvature of the universe and provide a great deal of information on the evolution of galaxies at different epochs.

The orbiting of an LST would be such a large undertaking

that its useful lifetime must be counted in decades. If the Space Shuttle should become available in the 1980s the desired maintenance capability would be assured. In this decade we may look to the launching of a half-scale prototype (1.5 m diameter) as a step toward the eventual LST.

Although European space astronomy seems to have abandoned plans for a large optical telescope in the near future, much emphasis is being placed on high energy astronomy. UK-5, a 270 pound spin stabilized X-ray astronomy satellite to be launched in 1973, will have improved capabilities over SAS-1. The European Space Research Organization (ESRO) has under consideration a lunar occultation satellite with a 200,000 mile apogee. Its X-ray detector will aim a 3° field of view at the Moon and thus observe a large number of source occultations with second of arc precision. Plans for small X-ray astronomy satellites are also going forward in Japan and the Netherlands; Soviet Cosmos satellites have carried X- and gamma-ray detectors as has Lunakhod-1. Undoubtedly such programmes will be further developed in the decade.

The first quarter century of astronomy from space platforms has brought us to a new generation of very advanced spacecraft and payloads and substantial opportunities for more effective use of rockets and balloons. From the modest vision of the small band of scientists who formed the V-2 Atmospheric Research Panel in 1946, we have come to the imminent realities of "Palomars" in space and the prospects of probing deeply into the universe in every wavelength of the spectrum.

CANADA

Science Policy and Canadian Manufacturing Industries

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This article examines the factors which determine the amount of research and development undertaken in Canadian industry and suggests that the influence of multinational corporations must be carefully incorporated into future science policy.

"MAJOR emphasis must be placed on the importance of using science and technology in support of the nation's social and economic goals". In its fourth report, *Towards a National Science Policy for Canada*, the Science Council of Canada in 1968 thus directed its attention along a path which brought its interests closer and closer to the topics of current debate. The council's work in the past three years has focused on the application of science and technology to such important problem areas as urban development, the natural environment, transportation, resource use and computerized communications. Most recently, the council has been primarily concerned with the problems of innovation in Canadian industry. Rather than attempt to review all the problems of today's Canadian science policy debate, I shall concentrate on the set of inter-related issues that dominate our concern about Canada's industrial science and technology. These are (i) the lack of traditional employment opportunities for highly qualified manpower¹; (ii) the cessation of growth and now the decline

of industrial research and development activity in Canada¹; (iii) the difficulties of Canada's high-technology manufacturing industries², particularly following the imposition of the United States import surcharges in August; (iv) the pervasive influence of the chiefly USA-owned foreign corporations which dominate the high technology sector of Canadian industry³.

The work done so far has failed to uncover any sound economic theory which could indicate whether or not there is some fixed minimum proportion of a country's economic activity which should be devoted to manufacturing. Perhaps such a minimum does not exist and policies in Canada should be geared entirely to the resource and service sectors of the economy; but nothing convincing has been written to shake the intrinsic faith in the idea that there should be at least some manufacturing activity, preferably in the higher technology areas, to provide stimulus and challenge to our increasingly well educated labour force. It is the sign of weakness in this activity which prompts the current concern.

Employment Prospects

Canada continues to have an unusually high annual growth in her labour force. It was 2.5 per cent a year during the past decade, for example, compared with 1.5 per cent in the United States, 0.4 per cent in Britain; the even more rapid increase in the proportion of highly qualified scientists and engineers in the labour force has been particularly marked during the 1960s. Following the 1961 census which exposed Canada's considerable dependence on immigration as a source of trained

people, it has been explicit government policy, at both federal and provincial levels, to expand university facilities, enrolments and opportunities for postgraduate research. The success of this policy is now evident; in 1970 Canada's per capita output of PhDs in science and engineering finally exceeded that of the United States. The problem of the supply of highly qualified people in many fields has been successfully overcome, so much so that a new problem has now emerged because Canada has failed to generate a high enough demand for such people, particularly in the traditional employment areas of research and development, and has failed to identify new ways to make use of them.

Demand for Manpower

The late 1960s and early 1970s have seen the three traditional sources of employment in the field of research and development dry up simultaneously. Hiring by government departments and agencies was cut back to a mere trickle following the government's decision in 1969 to impose austerity budgeting as part of its fight against inflation. The rate of expansion of university staffs, which has been about 13 per cent throughout the 1960s, was abruptly moderated and is now about 5 per cent, so the universities are absorbing a significantly reduced fraction of their own output. This leaves the industrial research and development sector which will be the principal focal point of this article.

In 1968 and 1969 Canada's industrial research and development activity reached a peak (at an expenditure level of about \$410 million) and has, in real terms, slowly declined since then¹. As so much attention has in the past been devoted to research and development in Canadian industry, this decline must be seen as a serious setback for existing policies. Of 36,000 industrial corporations in Canada only 640 have any research and development activity at all and more than 500 of these have ten or fewer professional (that is, graduate) employees engaged in this type of work. It is revealing to note that the 1970 output of science and engineering PhDs in Canada exceeded the entire stock of PhDs working in industrial research and development in the country.

Concern that Canada has been "doing too little research and development in industry" has been rife since the OECD started publishing comparative statistics on research and development in member countries in about 1963. Not only did Canada's gross expenditure seem too low (about 1.4 per cent of GNP) but the fact that industry accounted for only about one-third of it was taken to indicate a significant structural problem in need of a remedy.

Canada's federal government adopted an approach to remedy the situation which was unique in the Western world, when it enacted a series of "incentive programs"; these have been evolved over several years and the principal ones at present are the Program for the Advancement of Industrial Technology (1965) and the Industrial Research and Development Incentives Act (1967). These programmes relegated government to a passive role of provider of some assistance to research and development programmes devised by industry, in the form of grants or forgivable loans—forgivable, that is, if the project failed. Other countries have tended to cast government in the more active role of purchaser of research to meet goals designated by government. In retrospect, the Canadian incentives had some unforeseen flaws—they were tied to short term increments of growth of research and development activities and no support was given to the stabilization of existing activities; they also failed to consider the provision of a market for any successful innovation, a market which government purchasing power might have assured. When economic circumstances worsened, industrial research and development failed to command a share of many corporate budgets.

Manufacturing Industries

The Science Council of Canada recently published a report² which attributed the current malaise in Canadian manufacturing

Table 1 Foreign Ownership, Foreign Control and Research and Development Performance Distributions in Canadian Manufacturing Industry

	Foreign ownership (%)	Foreign control (%)	Distribution of industrial expenditures on research and development (%)
Electrical	70	78	29.1
Chemical	66	80	23.6
Transportation	82	80	17.8
Metals	51	51	9.8
Machinery	62	54	4.2
Pulp and paper	53	48	4.5
Utilities	18	4	11.0
Miscellaneous	50	59	

This topic is discussed at length in ref. 3.

to a series of problems. These were principally: (a) the inadequacy of the technological base of most companies; (b) the fragmentation of the domestic market for many products and the existence of barriers which inhibit entry into export areas; (c) the inadequacies of the management of many Canadian enterprises; (d) the poor climate for investment in Canada (reflected in the excessive caution of Canadian investors); (e) the improper location of some industries. The first three of these problems are aggravated by the dominating presence of foreign owned corporations in Canada's economy.

Foreign Ownership

To encourage the growth of employment opportunities Canada has traditionally offered tariff protection to resident industries and has encouraged direct foreign investment throughout the economy. The net effect of these twin policies has been the emergence of an unusually high proportion of foreign owned and controlled industries in Canada, particularly in those sectors where most Canadian industrial research and development is performed (Table 1).

The traditional conclusions drawn from such data have usually stressed that foreign corporations have been doing more than their fair share of research and development in Canada. Further study of the situation has indicated that such a conclusion is simplistic, and that a case can be made that Canada is suffering from the unforeseen and adverse effects of a surfeit of "technology transfer" which previously had been regarded as an unmixed blessing. The most important manifestation in Canada of foreign ownership is the extensive presence of subsidiaries of large multinational corporations and it is through these enterprises that technology transfer most frequently occurs.

The success of the multinational corporation is often ascribed to its ability to manage technology. Having invested large sums of money in the development of a new product or process, it is in the interest of the corporation to maximize its returns on this investment by transferring the new technology into production in as many locations as possible. The "higher" the technology, the bigger the investment needed and hence the greater the incentive to establish production subsidiaries abroad, behind tariff walls. This logic may well lie at the root of the large concentration of foreign ownership in Canada's high technology manufacturing sector.

The typical Canadian branch plant subsidiary possesses little "technological depth"; it is not set up in a manner which permits it to innovate but rather it receives most of its technology from its parent—production drawings, materials specifications and even specialized parts flow into the Canadian operation from abroad. As an example of this lack of depth, at least one of "Canada's" chief automobile manufacturers imports a team of engineers from the United States each year to carry out annual model change modifications to its production line. Under such conditions there is little scope for individual management initiative and the spirit of the entrepreneur is stifled.

The advantage of technology transfer to the branch plant

is a substantial reduction in the overhead charges associated with the generation of new technology, which in turn allows the subsidiary to exist while having only a small share of the Canadian market—a share which would be too small to support a domestic corporation which depended on generating its own technology. Although a subsidiary may exist under such conditions and although its internal economics might make it appear globally competitive, it will often not have a mandate to seek export markets in which it might compete with the parent or a related subsidiary, so the opportunity to expand based on international trading is denied. In effect the subsidiary trades the option of exporting in return for transferred technology.

For such branch plant subsidiaries, their dependence on technology imported from a foreign parent has meant that they offer: (i) little or no employment of highly qualified people, especially in research and development, because there is no mandate to innovate; (ii) little or no opportunity for the development of aggressive management and entrepreneurial skills; (iii) a ceiling on overall employment imposed by the limitations of the demands of the Canadian market (21 million people); and (iv) substantial impediments to a domestic corporation breaking into the already badly fragmented Canadian market because the domestic corporation would have higher overheads associated with the development of its own technology.

Not all subsidiary operations are branch plants, however, and it is important to place in context the research and development efforts of the multinational corporations which operate in Canada. These efforts can broadly be classified as being one of two dominant types: (a) a small facility whose chief preoccupation is the scaling down of imported technology to suit Canadian tests, conditions and smaller markets, or (b) a highly specialized laboratory which may have no connexion with the production activities of the same company in Canada; any successful innovations emerging from such a “rationalized” research and development operation could lead to production in the parent country, the host country or some third country depending on which location would optimize the returns to the whole operation. In such a case a Canadian incentive grant for research and development could well be a subsidy for the creation of manufacturing jobs and profits in some other country. The whole operation creates a rather special kind of “brain drain” in which the individuals do not leave the country but their ideas do.

Strategies for Canada

The outcome of studies by the Science Council on industrial research and development has been a preliminary delineation

of the many influences of foreign ownership and multinational business which pose constraints on Canada's ability to take initiatives in the industrial sector. These problems are today perceived as political issues; they are widely debated and much studied, and a ministerial task force at the federal level has been investigating the implications of foreign ownership for Canada. Although different parts of the political spectrum may regard the existence of multinational corporations in our economy from widely differing points of view, all must recognize that these corporations are now an economic fact of life, that their influence on world trade may well grow and that each host country must find ways of ensuring that subsidiaries make an adequate contribution to the realization of the goals of the host rather than only to those of the parent or third nation. Control of the multinational corporation is difficult for both host countries and those countries in which their headquarters are located. The administration in the United States claims, for example, that United States investment overseas is equivalent to “exporting jobs”. To control their own multinational corporations the United States administration has backed a Bill, now before Congress, proposing the establishment of a “Domestic Industrial Sales Corporation” designed to offer tax incentives to corporations which “repatriate” manufacturing jobs.

For Canada, more than any other Western country, the need to learn how to live with the multinational corporation and to have it contribute to the country's goals is urgent. Experience has shown that the approach of the research and development incentive programmes has assumed that promotion of research would be a panacea, the source of improved productivity and ultimately of increased industrial activity and more jobs. This approach has not been successful and a new one is needed.

The Science Council of Canada has been strongly underlining Canada's need for a clearly articulated industrial strategy. Although the problems raised in this article need solution, they are not the only ones facing the would-be strategist and any final policy will be found only in the broader context of the nation's concern about the costs and benefits of industrialization, about employment, education and environment and about the fostering of social justice in the world today.

¹ Kelly, F. J., *Prospects for Scientists and Engineers in Canada*, Special Study No. 20 (Science Council of Canada, April 1971).

² *Innovation in a Cold Climate; the Dilemma of Canadian Manufacturing*, Science Council of Canada, Report No. 15 (October 1971).

³ Cordell, A. J., *The Multinational Firm, Foreign Direct Investment and Canadian Science Policy*, Special Study No. 22 (Science Council of Canada, in the press).

GEOPHYSICS

Alive and Well

from our Geophysics Correspondent

This article describes both the state of geophysics research in the United States and some of the directions in which it is moving.

It is quite impossible to give anything like a balanced account of the state of geophysics in the United States in the space of

a short article. All one can really do is declare it to be alive and well and point out some of the salient features, begging the pardon of those who are not mentioned. The American Geophysical Union has a membership of more than ten thousand and geophysics as a discipline covers everything from cosmic rays to seismology by way of planetology, hydrology, meteorology, volcanology, oceanography, tectonophysics and geomagnetism. So this article will describe a limited sample of geophysical activities, based on a personal predilection for the solid Earth.

Sources of Finance

Geophysics could not have reached its present healthy state without a large infusion of money and it is therefore worth looking briefly at the sources. The diversity of these sources is the strength of the science. One single national organization devoted to distributing research funds—the system that most countries have adopted—has many merits but the American system is a valid counter-example. If you have no luck with your grant application at the National Science Foundation you can always try the National Academy, the Advanced Research Projects Agency (ARPA), the Air Force, the Army, the Navy, the Atomic Energy Commission, the oil companies, the National Ocean Survey, NASA, several foundations and one or two favourably disposed millionaires. In recent years the environment movement has been given a perhaps undeserved boost by the establishment of geophysics departments in many smaller universities aiming to “cover” the environment with three or four diverse professors. Perhaps it is here that geophysics is showing signs of over-reaching itself. Some of those lured with promises of shining new departments are expressing disillusion at the expense of maintaining an adequate geophysics programme and the waning of university enthusiasm when it comes to fitting out laboratories and acquiring data; this at a time when the traditionally large earth science schools such as Columbia, Harvard, MIT, Berkeley, Caltech and San Diego are being themselves confronted with a decline in available funds. ARPA's project VELA, for example, which injected \$150 million into geophysics in the 1960s for nuclear test detection is now a rapidly shrinking programme. NASA is a doubtful quantity. The 1970 Mansfield amendment restrained military spending in universities. As yet the belt-tightening has not cut very deep, and good undergraduates continue to flow into the subject. A PhD in geophysics is still more in demand than a PhD in physics but the signs of levelling out are everywhere.

American geophysicists confine themselves to the continental United States no more than do American soldiers. This is perhaps most clearly seen in the marine sciences. Lamont, Woods Hole and Scripps, the traditional seagoers, have been joined by a score or more of other oceanographic institutes with their own deep-sea vessels. Most of these have identified some particular region as their own parish and few have opted for the nearest offshore region. Magnetic, gravity, heat-flow and air gun surveys are widely undertaken and magnetics, of course, has been the most profitable with its huge returns in the field of seafloor spreading. The JOIDES drilling programme has been a brilliant success in inter-university co-operation, and perhaps will lead to a more national approach to some of the geophysics projects (such as ocean bottom instrumentation) which are too complex for individual groups. Palaeomagnetism of cores is vigorously pursued and dredging seems to be losing its association with black magic. Seismic refraction, conversely, seems to be in decline, perhaps because of its expense and the frequent ambivalence of its results.

Availability of Data

The thing that strikes the visitor to any American geophysical laboratory is the sheer volume of data. This has made the American research worker much more able to capitalize on discoveries than his counterparts elsewhere. Perhaps this was most strikingly seen when plate tectonics burst onto the scene. Laboratories which had accumulated large amounts of magnetic data and which had access to the global data of the World-Wide Seismic Network were able to move in rapidly and, within a year or two, to have the subject remarkably well documented. Lamont-Doherty's extraordinary vigour in this direction is worthy of special note.

At the present D. Karig's ideas on the structure within island arcs is attracting much attention and, one suspects, papers are being written which give strong support to the concepts. Also J. Morgan's hotspot hypothesis is being

followed with interest but it suffers from a lack of crucial experiments which has as yet prevented its wholehearted acceptance. This bashfulness does not seem to extend to graduate students who, with customary enthusiasm, are explaining the world's remaining problems in terms of behind-arc-spreading and hotspots. One hopes that they are right. Apart from the hotspot hypothesis, causes of continental drift as opposed to its consequences are apparently receiving scant attention. This probably stems from the large amount of work required to determine stress fields in the mantle by comparison with the smaller amount necessary to explain the observed features of a small section of the globe by plate tectonics.

Seismology, traditionally the largest branch of geophysics, is at present in transition. The VELA programme is drawing to a close and the emphasis is shifting; with detection, location and identification as its prime concern, it was a shot in the arm for classical seismology and caused research on the mantle and the core to become an integral part of solving the problem. Now an excellent data base has been developed from individual stations, arrays and new generation instruments and classical seismology is well supplied for several years to come. The new topics of interest seem to be high pressure geology, the nature of earthquakes, their prediction and control. As seismologists have been making finer distinctions in their models of the mantle, it has become a question of growing interest whether certain deep boundaries that seem to exist fairly consistently throughout the world can be associated with changes in mantle composition under high pressure and temperature. A cognate and even more interesting question is whether, if the precise depth of these discontinuities is known, laboratory studies on “rocks” of different composition can indicate which composition is the most likely. O. L. Anderson of UCLA and D. L. Anderson of Caltech have played an important role in following up the early work of F. Birch of Harvard and several laboratories are now extensively committed.

Using Teleseismic Data

An equally flourishing programme on earthquake sources is in progress. There was a time when seismology could do little with teleseismic data from earthquakes except use them to determine Earth structure but the work of L. Sykes (Lamont) on reliable focal mechanisms changed the picture immensely. Now J. Brune (San Diego), K. Aki (MIT) and their students are providing a clearer picture of the fundamental parameters of an earthquake—size of fault plane, moment, stress, stress drop and rupture velocity. This is being done by a combination of teleseismic observations and “near-in” instrumentation for Californian earthquakes. This looks a very promising field, and one with almost unlimited scope because of the many different types of earthquake.

Many Americans were, of course, at the International Union of Geodesy and Geophysics in Moscow in August and one of the consistent impressions that they brought back was of the success that the Russians were having in earthquake prediction. Success in this context is not yet to be construed as more than an ability to forecast earthquake-prone regions as a function of time. The prediction programme in the United States has been centred on the San Andreas Fault, and the Earthquake Mechanisms Laboratory in San Francisco and the Geological Survey in Menlo Park have been prime movers. An impressive amount of instrumentation is now deployed along the fault for the study of micro-earthquakes and premonitory tilts and strains. Progress is being made but there are still some problems in store. This was made clear by the San Fernando earthquake of last February, an event which gave no premonitory signs and which occurred on a fault which few had even heard of. The speed with which geophysicists got to work on documenting the San Fernando quake was impressive; within a day, local networks had been

established to study aftershocks and, within two months, coherent accounts of the earthquake, its aftershocks and its effects were being presented.

As the physics of the earthquake source is pursued some startling new ideas are arising. The role of fluids in the vicinity of a fault is being increasingly appreciated as a result of both laboratory experiments and field observations. Tests are now being conducted in the Rangely (Colorado) oilfield by B. Raleigh and J. Healy of the Geological Survey which indicate that micro-earthquake activity is correlated with the fluid pressure in the fault zone. Pressures higher than hydrostatic pressure seem to unlock the fault in some way and to allow strain adjustments by means of earthquakes. The implications of these experiments for an earthquake control programme are obvious and it may not be long before geophysicists ask for a mandate to look at somewhat more significant fault regions.

Lunar Geophysics

The lunar geophysics programme throws out a healthy batch of problems. A lunar "crust" seems to be emerging from observations of well timed impacts of spacecraft on the Moon but the seismogram complexity is still far from resolved. The hour-long energy train recorded after impacts is generally attributed to a highly heterogeneous Moon full of scattering centres but the latest and most irreverent explanation is in terms of non-linear oscillations of the seismometer itself. Time, presumably, will tell. The discovery of periodicity in moonquakes is quite remarkable. Correlation with perigee is striking, and all the more surprising because years of research

on earthquakes have failed to reveal a single correlation with extra-terrestrial sources.

One of the quieter evolutions in American geophysics seems now to have been completed. Gravity and magnetics have theorems which limit the amount of interpretation which can be applied to observations of potentials and in general geophysicists work within the confines of these restrictions. Seismologists had no simple theorem and, particularly in the interpretation of the Earth's density and elastic properties, models spawned in the mid-1960s. Now, however, some restraint can be applied. The work of G. Backus and F. Gilbert (San Diego) on inversion has set limits to what a finite data set with assumed standard deviations can reveal about the Earth. No simple two line explanation can be given of what the implications are—the papers have to be read. R. Parker, also of San Diego, has extended the Backus-Gilbert work into the domain of electromagnetic sounding where the need of it may be felt in the near future with a substantial increase in the deployment of magnetometers.

Geophysics, presumably, continues to survive in the prospecting industry which is understandably unwilling to brag about new technology. One suspects, however, that since the swing to digital recording and controlled energy sources with all the associated new concepts they brought the emphasis has been firmly on routine implementation of good techniques rather than on further research into new methods. No survey, however inadequate, of American geophysics should fail to mention the excellence of the services provided by the National Ocean Survey (formerly Coast and Geodetic Survey) which acts as a stable backdrop to the frantic activity of the academic geophysical community.

GENETICS

Genetic Analysis of Developmental Mechanisms in *Drosophila*

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The fruit fly *Drosophila* is being increasingly used in embryological experiments. Because of its well known genetics, and the ease with which the larvae can be manipulated in a variety of ways, it provides an ideal system for following such processes as cellular determination during differentiation, and cloning in morphogenesis.

WHEN Thomas Hunt Morgan left embryology for genetics he deserted *Hydra*, planaria, sea urchins and amphibia for *Drosophila*. The fruit fly was recognized, and still is recognized, as an ideal organism for the study of eukaryote genetics, but it now seems that it will turn out to be equally suitable for

answering many questions concerned with development. The fact that the *Drosophila* genome is midway in size and complexity between that of *E. coli* and that of mammals¹ makes this organism a logical choice for analysing the molecular biology of development, just as *E. coli* was a logical choice for analysing the molecular biology of heredity. The possibilities of *Drosophila* in the study of developmental biology were realized long ago by Stern, Hadorn, Poulson, Bodenstein and others. In recent years, however, interest has increased and we wish to review some recent trends in the analysis of its development.

Drosophila, like all holometabolous insects, lives what Snodgrass² has called a "double life"; that of the larva and that of the adult. After the completion of embryonic development (about 22 hours after fertilization) the resulting larva hatches and enters a growth phase lasting about four days. The larva then transforms to a pupa, and during the succeeding four days completes its metamorphosis to form the adult. During metamorphosis many of the larval tissues break down and most parts of the surface of the adult are constructed from small nests of cells in the larva, known as imaginal disks. There is a disk



Fig. 1 Adult structures (thorax bristles; yellow, *singed*³ genotype) derived from nuclear transplants into unfertilized eggs. From Schubiger and Schneiderman¹⁴.

representing each adult leg, one for each wing, and so on. These imaginal disks are set aside early in embryonic life and never become a functional part of the larva. They grow in size as the larva grows but they remain undifferentiated; their cells resemble those of embryos. Much of the recent research has been concerned with these essentially embryonic tissues as well as with the embryo itself.

The Embryo

The eggs of insects do not undergo cleavage in the usual sense. In *Drosophila*³, the cleavage nuclei undergo about eleven rapid divisions without separation of the cytoplasm into cells. About two hours after fertilization the nuclei enter the peripheral cytoplasm—the cortex—at a stage known as preblastoderm. At this time the nuclei probably begin to synthesize RNA⁴. Then they become separated by cell membranes to produce the cellular blastoderm embryo. This stage is shortly followed by gastrulation and the remainder of embryonic development. Most of the recent work on *Drosophila* embryology has been concerned with the early stages, and in particular with the question of when during development the cells or nuclei become determined to construct particular parts of the larva or adult. That is, when do their developmental capacities become firmly established?

A strong impetus to these studies has come from the findings^{5,6} that parts of embryos can be grown in the abdomens of adult flies. These parts complete embryogenesis in these conditions, and produce recognizable larval structures as well as tissues which will differentiate into adult structures when transplanted to host larvae for metamorphosis. This discovery greatly extends the possibilities for experimental embryology

with *Drosophila*, because pieces of the embryo can be manipulated in various ways without the necessity of ensuring the survival of the whole embryo. Using this technique with the 10 h embryo, Schubiger *et al.*⁷ were able to show that head structures and genitalia were formed only by cells from the anterior and posterior embryo halves, respectively. Hence, the different regions of the antero-posterior axis of the embryo had by that time become determined. More recently, Chan and Gehring⁸ have applied this technique to the embryo at the blastoderm stage, and they have shown that the anterior and posterior halves of an embryo at this early stage are already determined for the anterior and posterior structures of the adult, respectively.

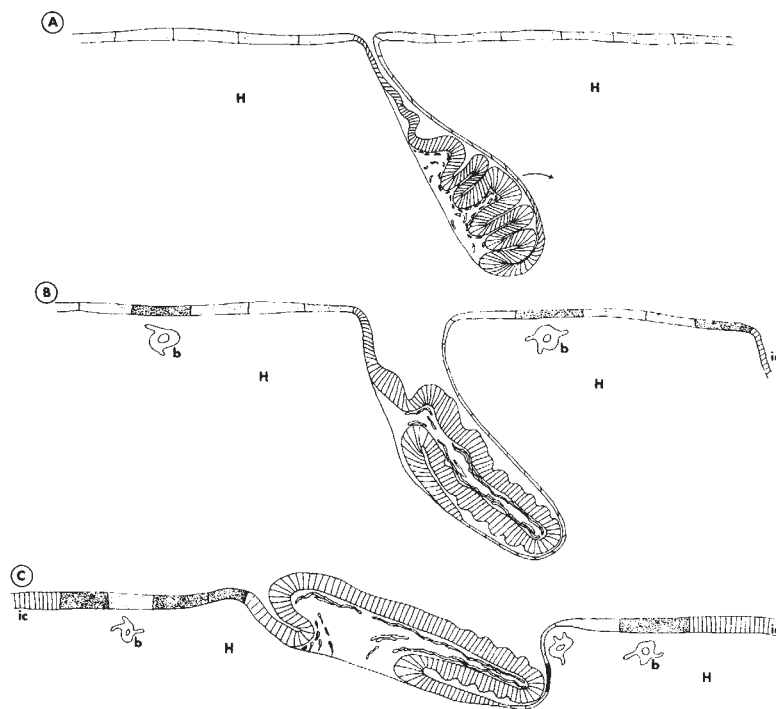
The evidence for determination at the blastoderm stage, coupled with evidence from other insects indicating that the cleavage nuclei are multipotent, has suggested to several workers that the basic pattern for the embryo may be established in the cortical cytoplasm even before the cleavage nuclei enter it⁹. The cells would then acquire their different determinations as the nuclei come to lie in diverse microenvironments within the cortex. It has been assumed that this is the case chiefly as a result of experiments indicating that a special region of the cortex of the egg, known as the pole plasm, influences the immigrating nuclei such that this region gives rise to the germ cells. Irradiation of this region of cytoplasm with an ultraviolet microbeam invariably produces sterile animals¹⁰. The idea that regions of the cortex other than the pole plasm exert analogous influences on the remainder of the nuclei has never been tested critically, however. Attempts to test this hypothesis have been made both by analysing the developmental consequences of defects made in the cortex of young embryos, and by transplanting nuclei and cytoplasm between embryos.

In the most recent defect experiments by Nöthiger and Strub (unpublished), accurately localized ultraviolet microbeams were used to produce burns in the cortex of embryos at early cleavage stages. Adults with various defects were obtained, but there was no correlation between the position of the burn and the position of the resulting defect in the adult. These findings are in contrast to those of Illmensee (cited in R. Nöthiger and S. Strub, unpublished), who found a topographical correlation between the positions of punctures made later in preblastoderm embryos and the positions of defects in the resulting adults. Hence, if the cortex is organized so as to exert localized determinative influences on the immigrating nuclei, it seems that this organization must develop at some time between the early cleavage and preblastoderm stages. During this brief period of about 2 h, the basic pattern of the adult organism seems to be mapped out.

The technical *tour de force* of insect surgery, nuclear transplantation in *Drosophila* eggs, has now been achieved in several laboratories. Geyer-Duszynska¹¹ and Illmensee¹² first reported limited development of unfertilized eggs after injection of nuclei from cleavage stage embryos. No adult structures were produced, however. Illmensee¹³ and Schubiger and Schneiderman¹⁴ have extended these experiments by culturing tissue from the defective embryos in adult abdomens. After transplanting this tissue to host larvae for metamorphosis, they were able to show that the transplanted nuclei had survived to eventually produce adult structures (Fig. 1). This was true whether the nuclei were injected into fertilized or unfertilized eggs. More recently, Zalokar¹⁵ has finally succeeded in obtaining adult animals from fertilized eggs which had been injected with nuclei. Genetic markers were used to demonstrate the participation of the implanted nuclei in the development of both larval and adult structures.

These successes open up a new field of experimentation in *Drosophila* developmental genetics. The technique can be used to prove or disprove the idea of the multipotency of cleavage nuclei. Furthermore, it should be possible to identify the factors that might produce specific microenvironments in the cortical cytoplasm, by transplanting pieces of cortex

Fig. 2 Diagram to illustrate the process of eversion in a leg disk. *A*, The disk epithelium in the mature larva is a single layer of epidermal cells, continuous with the larval epidermis through the disk stalk. *B*, 3–5 h after initiation of metamorphosis, the disk is partially unfolded and partially uncovered. *C*, 5–6 h after initiation of metamorphosis, the developing leg is almost completely unfolded and uncovered. Imaginal disk cells (*ic*) sequentially replace the larval epidermal cells. *H*, Haemolymph; *b*, blood cell. From Poodry and Schneiderman¹⁸.



between embryos and by implanting cytoplasm from differentiated cells into embryos. Further, one can begin analysing the processes of differentiation by means of the transplantation into eggs of nuclei from older stages.

Another approach to understanding the organization of the egg is through the study of mutants in which the homozygous female produces defective eggs. A particularly intriguing example is the mutant grandchildless of *Drosophila subobscura*¹⁶. The grandchildless females lay eggs whose pole plasm is abnormal, so that no germ cells are formed in the embryos, and the resulting adults are sterile. In *bicaudal* other parts of the egg are abnormal, so that embryos develop with two abdomens and no anterior parts¹⁷. Workers in several laboratories are searching for other mutants of this type, in the belief that studies of eggs with abnormal organization will provide clues to the mechanisms involved in normal development.

Imaginal Disks

The imaginal disks of *Drosophila* have recently attracted increased attention as model systems for the analysis of several developmental problems such as morphogenesis and pattern formation. As a basis for developmental and genetic studies several workers^{18–20} have studied the morphology of these organs and the morphological changes occurring during their development. The encouraging part of their findings is the simplicity of organization of the imaginal disks. Poodry and Schneiderman¹⁸ established that they are basically folded sacs consisting of a single-layered columnar epithelium. The disks also contain some nerve cells, and ad epithelial cells which are probably muscle precursors. Their origin in development as invaginations from the embryonic epidermis is consistent with this type of organization, and their change in shape to that of the adult structure (the process of "eversion") can easily be understood in terms of an uncovering and unfolding of the epithelial sac (Fig. 2). The conversion of the tightly folded epithelium of the disk to the extended adult structure represents a spectacular morphogenetic movement. This is especially true of legs, where it has been shown that the change in shape of the cell sheet is related to a change in cell shape from columnar to squamous¹⁸. Certain changes also occur in the cell junctions, the most obvious being a great increase in the number of septate desmosomes. Brief treatment with trypsin causes the

disk to undergo eversion *in vitro*, indicating that changes in intercellular adhesion, as well as changes in cell shape, may be important in causing the eversion movements²¹.

One of the reasons for our interest in imaginal disks is that their development can be analysed by the use of genetic mosaicism. The technique which has been particularly useful is X-ray induced somatic crossing over²². With this technique single cells in the imaginal disks can be made homozygous for recessive marker genes (for example, *yellow*, *singed*) while the cells in the rest of the animal are heterozygous (Fig. 3). All the progeny of the affected cells are also homozygous for the marker gene (or genes), so the resulting clones are recognizable as coherent patches of mutant tissue on the surface of the adult. Thus X-ray induced somatic crossing over permits the investigator to follow the developmental activities of the descendants of a single cell with great precision.

One striking result from these studies is that, in many parts of the adult, clones are markedly non-random in shape. The clearest case is that of the leg (Fig. 4) in which clonally related cells form long narrow strips of tissue often extending over several leg segments²³. Some clones have been found to be over 100 cells long without exceeding a few cells wide. This indicates that there is a predominantly radial alignment of daughter cells in the developing disk, which may be one of the important factors determining its structure. Similar longitudinal clonal patterns are present in wing disks^{24,25}.

Some scattered reports in the literature reveal that such clonal patterns are not unique to *Drosophila*²⁶. Spontaneous mosaics in wasps and bees show longitudinal stripes in the legs, and in wasps and moths similar patterns are found on mosaic wings. This leads us to conclude that oriented cell division may be a common feature of developing insect appendages. Furthermore, the fact that most clones are continuous and with smooth outlines persuades us that there is little individual cell movement in these systems.

Data from somatic crossing over experiments can be conveniently used to measure various parameters of imaginal disk development. Clone size in the adult depends on the stage of irradiation, because the number of cell divisions which are to occur before metamorphosis decreases with larval age. Hence the average clone size following irradiation at various stages can be used to estimate the cell numbers and rates of cell division in the disks at these stages. We have shown, for example, that the leg disk begins its developmental career as a

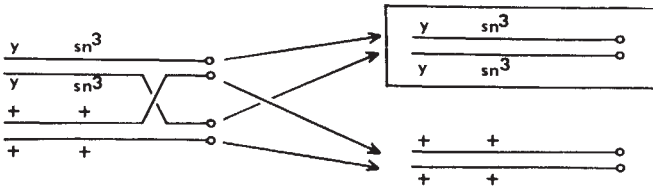


Fig. 3 Diagram to illustrate the process of somatic crossing over. Recombination between two chromatids from homologous chromosomes leads to homozygosity of the daughter cells. The *y sn*³/*y sn*³ daughter cell (boxed) produces a clone of cells with *y sn*³ phenotype, distinguishable from the rest of the animal which has a wild type phenotype.

group of about twenty cells in the embryo, and that it grows throughout larval life with an average cell cycle time of about 15 h, until the time of metamorphosis²³. The wing disk grows somewhat faster, with an average doubling time of about 11 h²⁴. The abdominal tergites represent an unusual situation, since the anlagen for these structures do not appear to increase in cell number during larval life, but do show rapid growth during the initial stages of metamorphosis (M. Guerra, J. H. Postlethwait and H. A. Schneiderman, unpublished, and personal communication from J. Merriam and A. Garcia-Bellido).

In the antennal disk, studies of the cell lineage pattern by Postlethwait and Schneiderman²⁶ have disclosed that its development is basically similar to that of the leg disk, but with the addition of several twists and bends late in development. The correspondence in developmental processes in the leg and

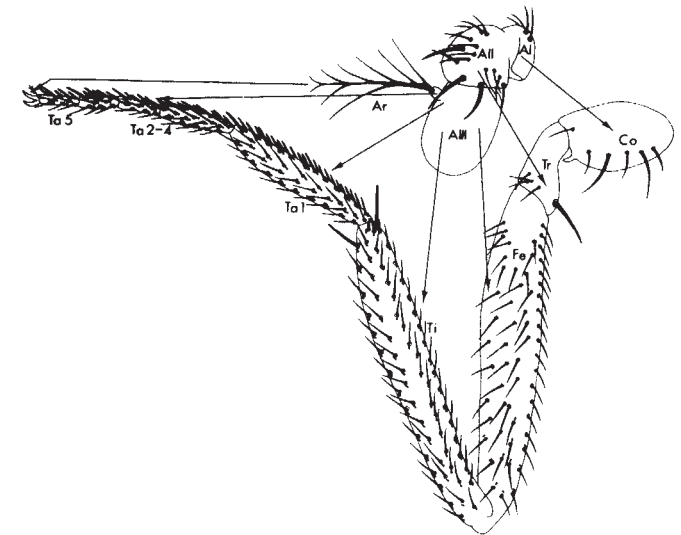


Fig. 5 The correspondence between the structure of the antenna and that of the leg, based on replacements in the leg-antennal intermediates of *antennapedia*. The third antennal segment corresponds not to one but to two leg segments. AI, AII, AIII, first to third antennal segments. Ar, arista. Co, coxa. Tr, trochanter. Fe, femur. Ti, tibia. Ta1-Ta5, first to fifth tarsal segments. From Schneiderman²⁷ and Postlethwait.

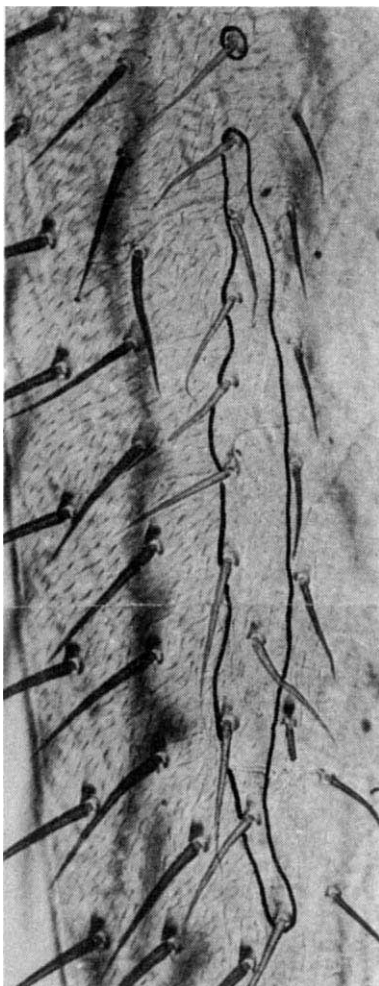


Fig. 4 A yellow; multiple wing hairs clone (outline) on the femur of the leg. *yellow* produces pale bristles; *multiple wing hairs* causes the epidermal cells to produce more than the usual one hair per cell. From Bryant and Schneiderman²³.

In view of the enormous literature dealing with the development of transplanted fragments of imaginal disks, it is perhaps surprising that much new information could come from the direct surgical approach. It is only recently, however, that the development of specific fragments of disks has been followed in detail, and this has disclosed an intriguing type of developmental organization in these structures. When pieces of a leg disk are implanted into the abdomen of host larvae of the same age, they metamorphose with the host and differentiate into recognizable, though unevolved, parts of the leg. Schubiger²⁹ has shown that the specific structures which are formed depend on which part of the disk is transplanted, so that he was able to construct a complete fate map of the disk. But more interesting are the experiments in which fragments of the disk are given extra time for growth before metamorphosis, either in an adult or a larval abdomen³⁰. In these cases one of two phenomena may occur: regeneration of the missing parts or mirror image duplication of those remaining. Furthermore, the capacity for these two activities is limited to certain regions of the disk. Regeneration is found in fragments containing one specific region, whereas duplication is found in fragments lacking this part. We have obtained similar results (Fig. 6) using a new technique of surgery *in situ* on imaginal disks³¹.

We have interpreted these surgical experiments to mean that cells in imaginal disks are graded in their developmental capacities. Cells at any one level in the gradient of developmental capacity can, given the opportunity for growth and cell division, replace only those parts which are normally at lower

positions in the gradient. When a disk is bisected, the cells at the two cut surfaces have similar developmental capacities, so that in each half they replace those parts of the system which are at lower levels. This leads to regeneration in one of the halves and duplication in the other. Recent experiments in which imaginal disk cells are killed by X-rays indicate that these gradients of developmental capacity are laid down in the disks at the very beginning of their development (J. H. Postlethwait, personal communication).

Similar theories have been proposed to account for the regenerative behaviour of the legs of other insects³², so for the first time we can begin to relate studies on imaginal disks of *Drosophila* to studies on the appendages of other insects. Indeed it seems that imaginal disks, although internal during larval life and temporarily relieved of the responsibility to secrete cuticle, retain many of the growth patterns and generative abilities of the appendages of less highly evolved insects.

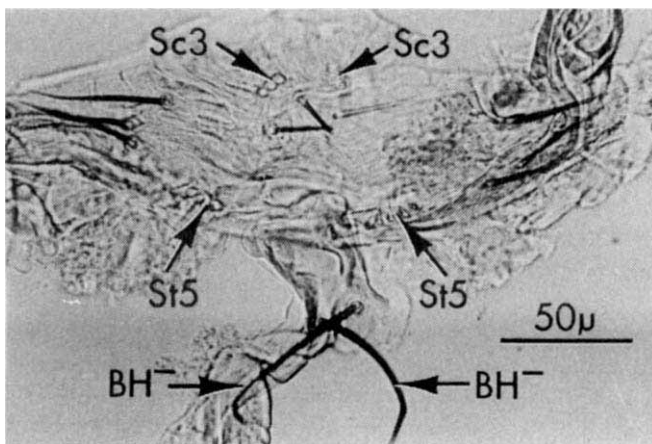


Fig. 6 Mirror image duplication of leg structures, caused by bisection *in situ* of the imaginal leg disk in the larva. Sc3 and Sr4 are specific sense organs of the trochanter, and BH⁻ is a unique bristle of the coxa. From Bryant³¹.

The process of growth regulation and pattern formation in imaginal disks are illuminated in a rather elegant fashion by a new lethal mutant we have isolated in which the imaginal disks undergo spontaneous duplication³³. The mutant is *lethal (2) giant disks (l(2)gd)*, and it is characterized by an extreme delay in the initiation of metamorphosis. During the extended larval period, the imaginal disks continue to grow and attain several times their normal dimensions (Fig. 7). The animals die shortly after the initiation of metamorphosis, probably as a result of the inability of these enlarged disks to undergo normal eversion. In mutant leg disks of older larvae not only extra growth but extra folding patterns appear (Fig. 8). Transplantation studies show that the extra folds represent a duplication of the anlagen in the leg disk, so that after metamorphosis two legs are produced instead of one. It is intriguing that the duplicate leg arises in that part of the disk which, as we know from surgical experiments on wild type animals, has the highest developmental capacity. It seems that this mutant in some way liberates a developmental capacity that usually remains latent.

Related to the problem of regeneration in imaginal disks is that of the reconstruction of patterns from dissociated disks³. Disks of two genotypes (for example, *yellow*; *singed* and *multiple wing hairs* leg disks) are mixed, treated with trypsin, and disrupted with a microstirrer. The disrupted disks are reaggregated by centrifugation and, after a short period of culture in an adult, are implanted into host larvae for metamorphosis. After metamorphosis, the implants often include familiar patterns (bristle rows, claw organs and so on) consisting of elements of both genotypes. A widely held view of this

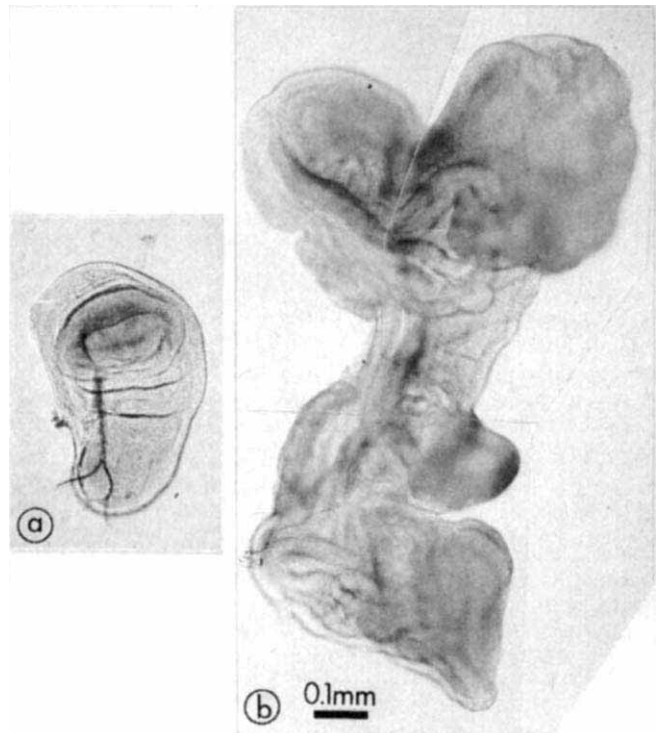


Fig. 7 Wing disks (a) from a mature normal larva and (b) from a homozygous *l(2)gd* larva 13 days after oviposition. From Bryant and Schubiger³³.

phenomenon was that the reconstruction of patterns is achieved by the migration of cells to their preassigned positions in the pattern. Such an interpretation was attractive at a time when the determination of imaginal disk cells was thought to be of a highly specific and rigid nature. But our findings of regenerative capacities in imaginal disks led Poodry *et al.*³⁵ to re-examine the process of pattern reconstruction. The conclusion from these studies is that directed cell migration is not the

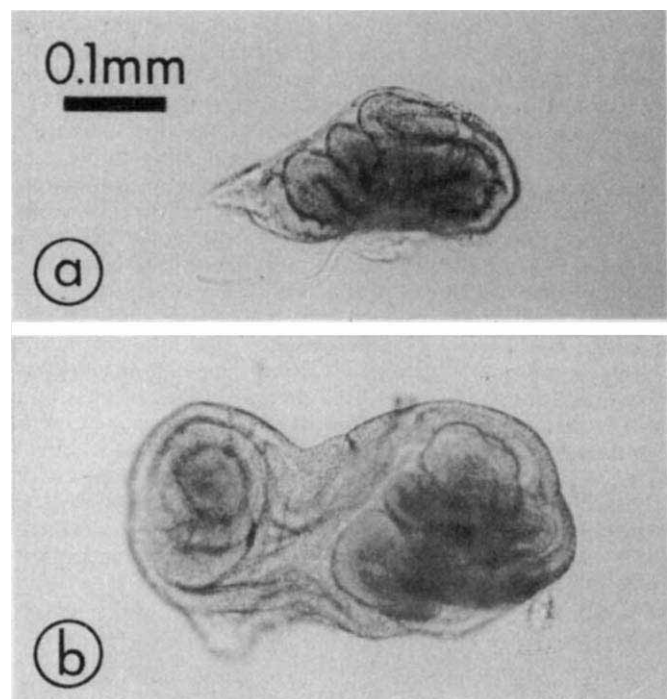


Fig. 8 a, Normal leg disk. b, Duplicated leg disk from a homozygous *l(2)gd* larva 9 days after oviposition. From Bryant and Schubiger³³.

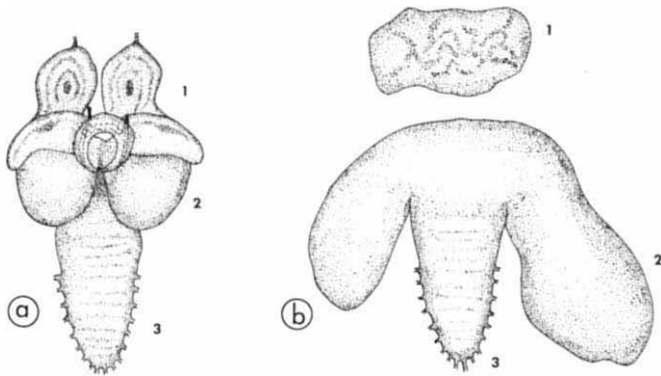


Fig. 9 Brain and eye-antennal disks from (a) mature wild type larva and (b) homozygous $l(2)gl^4$ larva. In the mutant the optic lobes (2) of the brain are overgrown, and the eye-antennal disks (1) are disorganized and fused. The ventral ganglion (3) appears to be normal. From Gateff and Schneiderman⁶.

mechanism for reconstruction, but rather that a considerable amount of "re patterning" occurs in the randomly reaggregated cell population. In our view, pattern reconstruction is a repetition of the events occurring during pattern formation in normal development, and as such can be used as a model system for the investigation of those events.

Transdetermination

It is becoming increasingly clear from many of the recent studies on imaginal disks that these structures are capable of a considerable degree of developmental regulation. Fragments of disks can, when allowed time for growth before metamorphosis, give rise to structures normally formed by other parts of the same disk. But even more remarkable is the ability of disk tissue to give rise to structures normally formed by different imaginal disks, by a process known as transdetermination. This phenomenon has been studied extensively by Hadorn and his collaborators³⁶, who have employed a technique of serial subculture of disk tissue using adult abdomens as culture chambers. Periodically, the developmental capacities of pieces of the tissue are tested by implanting into host larvae for metamorphosis. A common result from such experiments is that the tissue differentiates "autotypically" into structures characteristic of the disk from which it is derived. For example, tissue derived from a leg disk frequently produces sex combs and claw organs in the metamorphosis test. But the test pieces sometimes differentiate "allotypically" into adult structures other than those for which the donor disk was originally determined, showing that transdetermination has occurred during the growth of the tissue. For example, leg disk tissue was found to produce wings, thorax, antenna and proboscis²⁹. In other cases, the tissue became "atelo typical" and completely lost the ability to differentiate into cuticular structures³⁶.

These discoveries stimulated a number of workers to investigate the mechanism of the alterations. As a result there is extensive information about the developmental capacities of imaginal disk tissue after prolonged *in vivo* culture. It has been shown that the process of transdetermination may occur in populations of contiguous cells rather than in single cells³⁷. It has also been demonstrated that the process depends on cell division³⁸. The mechanism still remains as elusive as the mechanism of determination itself, however. New methods for culture *in vitro* may provide a new route into the analysis of this phenomenon.

Neoplasms

Insects differ from vertebrates in the almost total absence of neoplasms or cancers. Indeed as late as 1967 not a single lethal, transplantable and invasive neoplasm had been found in any insect. Approximately 400 papers had been published describing tumours in insects, but Harshbarger and Taylor³⁹

examined the available material and concluded that none of these tumours are comparable with the neoplasms found in vertebrates, a conclusion now shared by most students of the subject. A few of the tumours of *Drosophila* such as those occurring in the *female-sterile* and *fused* mutants⁴⁰ show rapid growth of specific cell types but the growths are not highly invasive. We have found that "tumorous head" outgrowths are in fact homoeotic changes in which parts of the head are replaced by parts of abdominal tergites, genitalia, and legs (J. H. Postlethwait, J. H. B. and G. Schubiger, unpublished). "Melanotic tumours" seem to be little more than accumulations of blood cells at various sites⁴¹. None of these so called tumours is invasive or lethal to the host, nor have any been subcultured as have many of the tumours of vertebrates.

About three years ago Gateff⁶ discovered two neoplasms in the mutant *lethal (2) giant larva* ($l(2)gl^4$) of *Drosophila*. One of these is a lethal, malignant, and invasive neuroblastoma of the larval brain (Fig. 9). It can be repeatedly subcultured in adult abdomens for many generations, in which it is also malignant and invasive. It is the first invasive and lethal neoplasm found in invertebrates and it shares many features with malignant neuroblastomas of vertebrates. The second neoplasm found in $l(2)gl^4$ is a lethal but non-invasive neoplasm of the imaginal disks. The imaginal disks of $l(2)gl^4$ larvae are very disorganized (Fig. 9) and fail to metamorphose into cuticular structures when transplanted into normal larvae. When transplanted into adult hosts the $l(2)gl^4$ disks grow rapidly into compact structures and cause the death of the host within 7–14 days. Both neoplasms show histological and morphological changes typical of neoplastic cells in general, such as reduced intercellular contacts, nuclear deformation, and changes of the cell and nuclear membranes.

The discovery of these neoplasms led us to examine the general question of tumorigenesis in insects. We propose that the infrequent occurrence of true neoplasms in insects (in contrast to vertebrates) is a consequence of certain peculiarities on insect development, notably the absence of cell division in most adult tissues and in many larval tissues, the destruction of many larval tissues during metamorphosis, the frequent occurrence of polyploidy and polyteny, and the relative stability of the karyotype. It seems that neoplasms develop in *Drosophila* chiefly as a result of genetic mutations, and that genetically induced neoplasms can be expected to occur in situations where there is rapid cell division, such as in the embryo, and in the imaginal disks and nervous system of the larva.

We have recently begun to look for neoplasms among embryonic lethals, and the results have been encouraging. Gateff (personal communication) has shown that the nervous system of the well known embryonic lethal *Notch* ($Df(1)N^8$) is neoplastic and promptly kills hosts which receive transplants. Unlike the neuroblastoma of $l(2)gl^4$, the *Notch* neoplasm consists not only of neuroblasts but also of other cell types present in the embryonic nervous system. We have also examined several mutants which have defective imaginal disks and brains, and which die during the larval-pupal transformation. One of these, $l(2)gd$, gives rise to a brain neoplasm very much like that of $l(2)gl^4$, but the mutation is at a different locus on the second chromosome³³. Since it appears that we can induce and select large numbers of mutants which might produce neoplasms in *Drosophila*, we may be able to identify the genetic change responsible for a particular cancerous property. The elucidation of the mechanisms of neoplastic transformations in this system would surely be relevant to an understanding of cancers in other systems. We know of no system in higher organisms in which the genetic changes underlying neoplastic transformations can be examined as easily and in as much detail.

Selection of Mutants

An important approach to developmental problems using *Drosophila* involves the selection and analysis of large numbers

of mutants affecting particular developmental or physiological processes. By studying the ways in which mutations can modify these processes, we hope to reach an understanding of the genetic control of the processes in the normal situation. Wright⁴² has recently reviewed the progress being made in the application of this approach to particular aspects of embryogenesis. In addition, the development of imaginal disks is being studied in this way in several laboratories. Recently Shearn *et al.*⁴³ have selected and examined 134 lethal mutants in which death occurs during metamorphosis, and have found that nearly half of them have defective imaginal disks. In some of these, the imaginal disks are absent and in others they are morphologically abnormal. In some other mutants the disks appear morphologically normal, but are unable to metamorphose properly when transplanted into normal host larvae. Stewart *et al.*⁴⁴ have been working along similar lines, using a technique for assessing the developmental capacities of the disks *in vitro*.

The experiments on late larval-pupal lethals indicate that the larval organisms can tolerate almost any kind of defect in the imaginal disks including their complete absence. Hence the selection of such mutants should make it possible to analyse rather completely the genetic control of imaginal disk development. The fact that mutations like *l(2)gd* can have profound effects on the disks without impairing the viability or structure of the larva emphasizes the genetic independence of the larval organism and the future imago. One can now investigate the possibility of distinct larval and imaginal gene sets, each capable of separate evolution, as proposed by Wigglesworth⁴⁵.

The application of the mutant selection approach can be greatly extended by the use of conditional mutants which show the mutant phenotype in certain (restrictive) conditions and the normal phenotype in other (permissive) conditions. Considerable effort is now being devoted to the collection of two types of conditional mutants in *Drosophila*: those which are temperature sensitive and those which are nutrition sensitive.

Suzuki and his colleagues⁴⁶ have recently shown that the use of the powerful mutagen ethyl methane sulphonate (EMS) permits the isolation of large numbers of temperature-sensitive lethal mutants. As a working hypothesis it is assumed that these mutants are of the missense type, and that this leads to amino-acid substitutions in polypeptide chains which render them thermolabile. The conditional nature of these mutants permits the definition, for each of them, of a period of development during which the organism is sensitive to the restrictive conditions (usually high temperature; 29° C). Exposure to such conditions during the temperature-sensitive period results in subsequent death at the "lethal phase", but exposure at any other time permits survival. Hence, the study of these mutants allows the determination of the periods during which certain gene products are necessary for development. Most of the mutants studied have a temperature-sensitive period in the embryonic or late larval-pupal stage, indicating that many gene products come into use for the first time at these stages. This finding is consistent with the intense morphogenetic activities occurring at these times. Arking (personal communication) has now collected more than 100 temperature-sensitive larval-pupal lethals, many of which have imaginal disk defects, and some of which may prove to have endocrine deficiencies.

Nutritional conditional lethals (auxotrophs) have even greater prospective value than temperature-sensitive lethals in the analysis of the genetic control systems of eukaryotes. It is therefore surprising that only a few laboratories have taken up the challenge of producing these mutants. Several defined media have been devised for *Drosophila*, and conventional mutagenesis techniques should permit the isolation of mutants whose survival depends on the addition of supplements to these media. Vyse and Nash⁴⁷ were the first to report the isolation of mutants of this type. They produced three auxotrophic mutants, one of which (1308) required RNA for growth. This was later shown to be a requirement for both purines and pyrimidines, presumably as a result of a double metabolic block⁴⁸. A specific requirement of pyrimidines for growth has

been demonstrated in the mutant rudimentary by Norby⁴⁹. It is of interest that homozygous females of this stock are sterile, as is the case with several other auxotrophs (D. Nash and D. Falk, personal communication). Thus, female sterility may prove to be a convenient method of preliminary screening for auxotrophic mutants.

The availability of auxotrophic mutants of *Drosophila* will permit us to answer many of the questions which recent findings on microorganisms lead us to ask about higher organisms. We should be able to test whether there is close linkage of genes concerned with particular metabolic pathways; this needs to be settled before we can ask meaningful questions about the regulation of gene activity. Auxotrophs could be used to increase tremendously the resolution attainable in genetic fine structure studies. Furthermore, some technical advances may accrue from these studies. For example, a thymidine requiring mutant would be extremely valuable for DNA labelling. Some of the enzyme deficiencies may prove useful as genetic markers for tracing the cell lineage relationships of the larval organs and of the internal organs of the adult.

Prospects

In this brief survey of *Drosophila* developmental genetics, limitations of space have precluded the discussion of several key areas, such as the current intensive efforts to understand spermatogenesis⁵⁰, oogenesis⁴⁰, the control of genetic activity in polytene chromosomes⁵¹ and the developmental genetics of behaviour^{52,53}. Nevertheless, we hope to have conveyed an idea of some of the approaches being made toward an understanding of the development of *Drosophila*.

Clearly many of these approaches have only begun to be exploited. Somatic crossing over makes possible the introduction of mutant cells into developing embryos at specific stages of development and permits studies of the interaction of mutant and wild type cell populations. The use of this method to investigate the processes of intercellular communication which underlie pattern formation⁵⁴ still has great potential. The use of temperature-sensitive mutants and of somatic crossing over techniques shows great promise as general techniques for investigating the time of action of genes and gene products during development^{46,55}. The great improvements in cytoplasmic and nuclear transplantation techniques for *Drosophila* and the use of laser microbeams to alter the fundamental organization of the egg and embryo also hold immense promise. And underlying all of these are the six decades of intensive genetic work which now enable experimenters to dissect the development of *Drosophila*, gene by gene.

In the next few years we expect at least one important technical advance to be made in *Drosophila* developmental biology, and that is the perfection of techniques for culture *in vitro*. Until recently, only limited success had been reported with *Drosophila* tissue culture, but many workers have now reported encouraging results with cells from embryos^{56,57}. In fact, Schneider (personal communication) has now been able to culture cells which will metamorphose into adult structures when transplanted to host larvae. Such techniques will permit the long awaited biochemical analysis of many of the problems in the developmental genetics of *Drosophila*.

We thank colleagues whose traditions of cooperation and sharing of stocks and information make this field a joy to work in, and especially our co-workers in the Developmental Biology Laboratory and Center for Pathobiology for helpful discussions and suggestions. Research from our laboratory described in this report was supported by grants from the US National Science Foundation, the American Cancer Society, and the US National Institutes of Health.

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MOLECULAR BIOLOGY

Reverse Transcriptase, the DNA Polymerase of Oncogenic RNA Viruses

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The excitement aroused by the idea that transformation of cells by RNA tumour viruses might depend on the activity of a reverse transcriptase enzyme(s) specific to the virus has stimulated much research since the enzyme was discovered in 1970. But the questions of the physical identity and catalytic activities of the enzyme(s), its function in transformation and whether it is unique to RNA tumour viruses remain unanswered.

TEMIN's enzyme is now one of the most discussed and utilized elements in tumour virology and there is no need to go deeply into the history of his provirus theory^{1,2}, which led to the

search for and discovery of this enzyme³⁻⁹. Briefly, Temin proposed in 1964 that the genome of an RNA tumour virus must be transcribed into DNA (the "provirus"). His speculation was made to explain how an RNA virus produced a stable genetic trait, a characteristic passing from cell to daughter cell (namely neoplastic transformation). The DNA provirus in a double stranded form could then be integrated into host cell DNA. The discovery of the enzyme led to an extraordinarily rapid collection of information on its properties and on its distribution in tumour viruses¹⁰⁻¹² so that now it is virtually a marker for a transforming RNA virus.

The virion reverse transcriptase may be essential for viral replication and cell transformation but these points have not yet been established conclusively. Initially, indirect experiments indicated that RNA tumour virus replication required a DNA intermediate (virus specific)¹³⁻¹⁶. The subsequent discovery of DNA polymerases in all known RNA tumour viruses (see refs. 7 and 12 for recent summaries) and its apparent ability to transcribe all the viral RNA¹⁷ are in keeping with the role of this DNA polymerase in viral replication and cell transformation. Two approaches have been utilized to try to

provide more direct evidence of the enzyme's requirement. The first approach has been the use of mutants. Hanafusa¹⁸ isolated a mutant of RSV called RSV_a (O), which is non-infectious, cannot transform chick fibroblasts, and does not contain polymerase activity. The addition of an avian leucosis virus (ALV) (which replicates in but does not transform these cells) with RSV_a (O) resulted in transformed fibroblasts. The obvious interpretation is that inability of RSV_a (O) to replicate and transform chick cells is due to a mutation in the gene(s) specifying reverse transcriptase; in the presence of ALV, the RSV_a (O) is able to use the ALV enzyme and thereby is capable of transforming cells (phenotypic complementation). Ultimately, non-infectious virus was produced by the transformed cells and the obvious interpretation is that the polymerase is required for transformation but not maintenance of the transformed state. It has not been satisfactorily demonstrated, however, that the sole or primary effect in this mutant is on the reverse transcriptase, and the biochemical evidence for defective or absent enzyme was not definitive. For example, results from mixing experiments with mutant and wild type enzyme are consistent with the presence of an inhibitor in the mutant preparation. Further, DNA polymerase activity was recently found in a similar mutant¹⁹. It will be necessary to study several mutants and provide more detailed biochemical analysis of any detectable polymerase before definitive conclusions can be made on questions relating to the necessity of reverse transcriptase for initiation of transformation and for maintaining the neoplastic state. The second approach has been the use of inhibitors, rifamycin derivatives²⁰⁻²³, and streptovaricins²⁴. Streptovaricins, which are fair reverse transcriptase inhibitors, were reported to block transformation of mouse fibroblasts by MSV, and the inhibition did not seem to be due to toxic effects on the cells²⁵. The MSV effects on mouse fibroblasts, however, are measurements of viral replication rather than transformation²⁶. Therefore, the interpretation of these results should be limited to supporting the notion that the enzyme is required for viral replication, and the limitation of this conclusion is the possibility of non-specific inhibition.

More than 200 rifamycin derivatives have been studied for their effect on the viral and on purified cellular DNA polymerases²³. A spectrum of derivatives is available, ranging from ineffective to extremely potent inhibitors. After pre-treating virus (MSV) with different derivatives and then removing the compound (so that toxic effects on cells do not obscure the results), a direct correlation was found between inhibition of reverse transcriptase and loss of the capacity to transform rat cells (R. C. Ting, S. S. Yang and R. C. G., in preparation). Again, an argument can be made that factors essential to viral replication and transforming capacity other than the polymerase are also affected by the rifamycin derivatives, and coincidentally the inhibition of these factors parallels inhibition of the polymerase.

One problem is that some of the biochemical evidence does not favour a replicative function for the reverse transcriptase. For example, the size of the DNA pieces made is small; the amount of DNA synthesized relative to input 70S RNA is low, most of the DNA is produced from a relatively small region of the 70S RNA²⁷⁻²⁹; and most recently Wells *et al.* (unpublished work of R. D. Wells, R. M. Flugel, J. E. Larson, P. F. Schendel and R. W. Sweet) have shown that the AMV enzyme, like other known DNA polymerases, does not effect *de novo* initiation of a new DNA strand in templated reactions. These problems may, however, be peculiar to the *in vitro* systems used to study DNA polymerases; and the combined biological evidence strongly suggests that reverse transcriptase is the enzyme for replication of these viruses.

Properties of the "Purified Enzymes"

The enzymes from avian type C viruses, purified (AMV)³⁰ and partially purified (RSV)³¹, have molecular weights of

about 110,000 and, at least in the case of AMV, a second protein of 69,000 molecular weight is present. In contrast, a molecular weight of 70,000 was reported for the partially purified enzyme from RLV³². Whether a true physically important difference exists between avian and mammalian reverse transcriptases to account for this difference, or whether there is a more trivial explanation, awaits further studies.

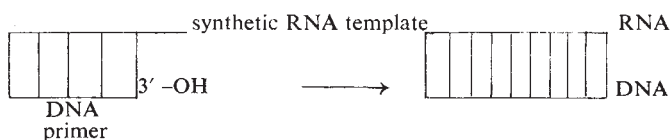
In a recent report it was concluded that the RNA and DNA template activities of reverse transcriptase were separate (two different enzymes)¹⁹, but this has not been the experience of others^{30,33}. Partially purified³³ and highly purified³⁰ enzymes have been found to retain the RNA, RNA-DNA hybrid, and DNA template activities, and competition experiments have shown that 70S RNA, RNA-DNA hybrids, and DNA compete with each other for the purified polymerase, supporting the view of one catalytic template site^{7,33}. Presumably then the one enzyme can carry out the following 2-step synthetic sequence:

Viral RNA → RNA-DNA hybrid → double stranded DNA

The double stranded DNA may then be integrated into the host cell DNA and when "turned on" may transcribe viral RNA molecules.

The template function of exogenous 70S viral RNA (with enzyme partially purified and separated from its own 70S RNA) merits further comment. Exogenous 70S RNA has so far been shown to template only with DNA polymerases of the avian viruses, RSV³³ and AMV³⁰. In similar assay conditions, activity has been considerably lower with the purified polymerases from the type B monkey mammary tumour virus and with RLV using 70S RNA from RLV or AMV. Lack of acceptance may be due to differences in enzyme primer requirements, template specificity, or low levels of contaminating RNAase. This is a particularly critical point with respect to negative results with cellular DNA polymerases and 70S RNA template activity.

The purified (or "crude") viral DNA polymerase does not accept single stranded synthetic homopolymeric RNA unless accompanied by a complementary oligonucleotide primer³⁵. The DNA synthesized with the template-primer complex is covalently joined to the primer^{29,35}, and the primer-product hydrogen bonded to the template RNA as shown below.



Recent experiments by Verma *et al.*³⁵, Wells *et al.* (unpublished), and Hurwitz (personal communication) have shown that the viral RNA may be both template and primer. The DNA product synthesized with a partially purified AMV DNA polymerase and exogenous AMV 70S RNA is covalently bonded to the viral RNA, perhaps as shown as mechanism 2 in Fig. 1. On caesium sulphate density gradient centrifugation (which separates RNA, DNA, and RNA-DNA hybrids) the labelled DNA product could not be separated from the viral RNA by heat denaturation. After alkaline hydrolysis (or RNAase) and heat, the product moved to the DNA region (J. Hurwitz, personal communication). These and other^{29,36} experiments have convincingly indicated that a covalent bond joins the DNA product to a template-primer RNA. At first glance these results appear to be at odds with earlier reports¹⁰ which indicated that after only heat denaturation the product moved from the hybrid to the DNA region. In the earlier reports, however, the whole viral "system" was utilized (disrupted virions with its endogenous RNA instructed synthesis of DNA), and these systems may have included an endonuclease. In the studies reporting evidence for the covalent bond, the enzymes were partially purified and the response to exogenous RNAs investigated. An endonuclease may therefore have been removed.

Potential Uses

(1) If reverse transcriptase is specific for RNA oncogenic viruses it is obvious that when appropriately assayed a positive result will support the notion that a particle is an RNA virus and at least suggests that the particle might be oncogenic. Every known oncogenic RNA virus tested so far contains this enzyme activity. This approach has already been utilized in two recent preliminary reports on human particles. (a) Reverse transcriptase is present in particles from human milk obtained from women with a familial history of breast cancer and from inbred populations³⁶. In this case there was some uncertainty that the particles were true viruses because they had not been grown in tissue culture and morphological studies were handicapped by other components in human milk. The evidence that these specimens contain reverse transcriptase considerably advances the notion that the particles are viral and potentially oncogenic. (b) The ESP-1 virus isolated from cells from the pleural fluid of a child with lymphoma and successfully grown in tissue culture by Priori *et al.*³⁷ contains reverse transcriptase³⁸. Because it was replicating in culture and could be carefully evaluated morphologically, no further evidence was really needed to show that the particle was indeed a budding RNA virus. In this case, the presence of the enzyme supports the concept that the virus may be oncogenic and further provides a tool for subsequent hybridization experiments (see below) that may more directly help to evaluate whether this or a similar virus actually plays a role in the pathogenesis of human tumours. It has not been proved that ESP-1 virus is of human origin³⁹, but the properties of the viral enzyme may help to clarify this point. The data which are required are: first, a careful comparison of the biochemical and immunological properties of the purified enzyme with the polymerase of the virus in question. The enzyme resides in virion cores, and therefore should not be subject to changes dictated by the recipient cell; second, by making labelled DNA copies of the respective viral RNA genomes (in this case murine and ESP-1) with their polymerases one can then compare the degree of hybridization of the DNA with the respective viral RNA as well as to cellular RNA (mouse and human). At present no definitive conclusion can be reached about the origin of ESP-1. (2) The enzyme may be useful for preparing highly radioactive DNA for hybridization studies. The DNA product of the endogenous RNA instructed reaction can be used to look for complementary sequences with cellular RNA. (3) Reverse transcriptase assays have been increasingly helpful as a rapid and sensitive method for identifying and quantitating known RNA tumour viruses. For an unambiguous measurement, contamination with cellular DNA polymerases should be slight (see below). The lower limits of sensitivity in most laboratories appear to be around 10^2 – 10^3 infectious units which is much more sensitive than electron microscopy.

Criteria

Even with best purification methods, however, cellular enzymes, including DNA polymerases, may contaminate viral preparations, and some minimum criteria are therefore needed for establishing the presence of "reverse transcriptase" in a virus or suspected virus. (a) The particle in question should be shown to band at the appropriate region in a sucrose gradient (approximately 1.16 g ml^{-1} for the type C viruses and somewhat higher for the type B), and the DNA polymerase activity must be in the same region. If virus is pre-treated with an appropriate concentration of non-ionic detergent, viral nucleoids (cores) are liberated and these band at a higher density (approximately 1.25 g ml^{-1}). As originally shown by Gerwin *et al.*⁴⁰ the polymerase will then band with the core. Higher concentrations of detergent (or high salt) may completely liberate the enzyme from other viral components so that the enzyme is now "free" at the top of the gradient. (b) The polymerase assays should initially include endogenous synthesis of DNA. This activity should be RNAase sensitive,

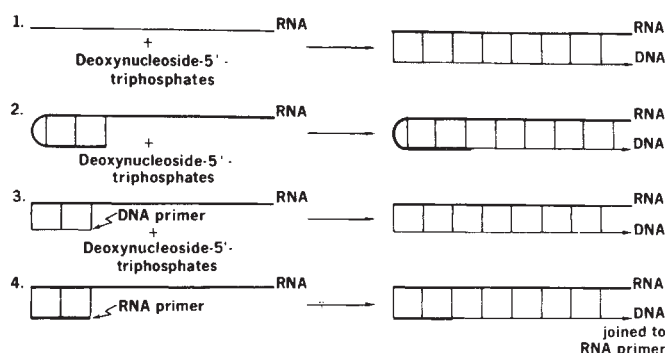


Fig. 1 Schematic illustration of possible biochemical mechanisms for step 1 (RNA $\rightarrow$ DNA) of viral reverse transcriptase. In mechanism 2 the 70S RNA has a complementary region with free 3'-OH and which acts as the primer for synthesis of DNA directed by the remaining RNA template. Mechanisms 3 and 4 would add importance to small RNA and DNA molecules that may be present in the virus.

require disruption of the virus, and require the presence of all four deoxynucleotides and magnesium. The conditions for RNAase sensitivity are of some importance. High RNAase concentrations with no salt will degrade double stranded RNA or RNA of RNA-DNA hybrids. It would be preferable to show sensitivity with relatively low RNAase concentrations (10 – $20 \text{ } \mu\text{g ml}^{-1}$) and high salt (0.2 M). In these conditions most RNA hybridized to DNA should not be susceptible to RNAase. Sensitivity to RNAase can then be assumed to result from degradation of single stranded RNA, a more specific template for viral polymerase than DNA-RNA hybrids (see below). (c) Analyses of the product should include proof that the product is DNA and that at some point in synthesis the DNA is hybridized to RNA. Most investigators have shown this with equilibrium centrifugation in caesium sulphate density gradients. DNA products of early synthesis band in the RNA region. With increasing time of incubation the product moves to the region characteristic of DNA^{10,41}. The most definitive evidence for a viral reverse transcriptase is that the DNA product specifically hybridizes to viral 60–70S RNA. Again, this is generally carried out by equilibrium centrifugation after initial isolation of the DNA product, removal of RNA, and hybridizing the DNA back specifically to the viral RNA. (d) Exogenous templates, antibodies, and inhibitors are useful in preliminary detection of the viral enzyme and in proper combination they may provide a rapid and easy assay which is reasonably conclusive.

Synthetic Templates

The viral enzyme has relative affinity for double stranded synthetic homopolymers containing one polydeoxyribonucleotide strand and one polyribonucleotide (for example, poly dT-poly rA and poly dC-poly rG)¹¹. Enhancement of sensitivity of detection has made them useful in preliminary searches for the viral enzyme as initially advocated by Spiegelman⁴². It is quite clear, however, that these polymeric hybrid templates are not specific. Every purified DNA polymerase investigated, including those from *E. coli*^{34,43}, *Micrococcus luteus* (unpublished work of R. D. Wells, R. M. Flugel, J. E. Larson, P. F. Schendel and R. W. Sweet), normal fresh blood human lymphocytes (R. G. Smith and R. C. G., in preparation), normal mammalian cells in tissue culture⁴⁴, and calf thymus⁴³, accepts these templates very well. Even in preliminary surveys their usefulness may be limited. For example, some crude preparations of virus or virus heavily contaminated with Mycoplasma have shown minimal response. This was true with the polymerase from two potential candidates for human tumour viruses, the milk particles³⁶ and ESP-1³⁸, and is probably due to nucleases. Baltimore compared template preferences of DNA polymerase I of *E. coli* and the AMV

enzyme³⁴. He concluded that although the *E. coli* enzyme will "read" off the ribohomopolymer strand of a hybrid template, it has marked preference for the deoxyribomopolymer strand. Comparing the DNA polymerases of AMV, *E. coli*, and *M. luteus*, Wells *et al.* (unpublished) find for all three: (a) there is preference for double stranded polynucleotides (DNA preferable to RNA); (b) DNA-RNA hybrid polymers are suitable template (primers); and (c) double stranded synthetic RNAs serve (but poorly). In short, there was little if any selective acceptance of polymeric duplex templates with AMV compared with bacterial DNA polymerases. Natural RNA templates were not studied.

Templates that Distinguish

Combinations of synthetic primer oligomers with homopolymeric templates (with excess template to primer) allow one to distinguish the viral enzyme from other DNA polymerases. This is particularly true with oligo dT·poly rA and oligo dT·poly dA with TTP as substrate. For example, with the AMV enzyme oligo dT·poly rA is about 50 to 100 times more active than oligo dT·poly dA⁴⁴. Conversely, the DNA polymerases of *E. coli*^{29,34,47}, *M. luteus*²⁹, calf thymus⁴⁶, and normal human lymphocyte DNA polymerase I and polymerase II (R. G. Smith and R. C. G., in preparation) all show marked preference for oligo dT·poly dA.

Viral and the principal mammalian and bacterial DNA polymerases can also be distinguished with natural RNA templates, in particular the single stranded viral 70S RNA. Although 70S viral RNA is not as effective a template as some of the synthetic DNA and DNA-RNA hybrid templates or natural "activated" DNA it will work with the viral enzyme but to a relatively small degree or not at all with other tested DNA polymerases⁴³. It is apparent then that the appropriate use of templates may distinguish between purified viral and cellular enzymes. It should be noted, however, that enzymes that may be viral in origin may not give the appropriate template response if significantly contaminated with nucleases.

Antibodies

Aaronson *et al.* have obtained antibodies against viral (mouse) reverse transcriptase⁴⁵. The antibody has cross-reactivity against the polymerase from some mammalian type C RNA viruses, for example, cat, rat and hamster, but not against polymerase from avian type C or any "type B" RNA virus⁴⁶. The antibody did not cross-react with two major DNA polymerase activities from tissue culture cells, so it was proposed³³ that this antibody could be used to ascertain if any DNA polymerases found in human leukaemia were from mammalian leukaemia virus. This approach is based on several assumptions. (1) The two activities found in normal cells are assumed to represent the only DNA polymerases, that is, that no polymerase was missed in isolation attempts. In view of the very late discovery of DNA polymerases II and III in *E. coli*, this cannot be taken for granted. (2) That two activities represent two separate DNA polymerases. The evidence for two proteins was two separate activity peaks on columns. Because these were not highly purified enzymes and protein peaks were not shown in their report, this could represent one DNA polymerase contaminated by activators and inhibitors that vary in their column elution and account for spurious peaks. (3) Antibody may have been directed against adventitious factors required for maximum polymerase activity rather than against the polymerase. These factors may not be required to the same degree for an enzyme of another source. This is a serious pitfall when antibody is prepared against proteins not purified to homogeneity. (4) Finally, and most significant, it is assumed in this approach that an antibody to a mouse viral enzyme will cross-react with a potential human viral enzyme. Since cross-reactions were not found with type B virus, a putative human leukaemia virus would have to be of the C type. In any event, recent information⁴⁷ indicates

that the mouse antibody did not cross-react with the polymerase from a newly isolated type C monkey virus. The lack of applicability of this mouse antibody approach to human tissues is now clear.

Inhibitors

There have been several reports of inhibition of reverse transcriptase by various compounds, particularly rifampicin derivatives^{20-23,48}, streptovaricins²⁴, ethidium bromide, daunomycin, and related compounds^{49,53} and most recently poly rU⁵¹. What are needed, of course, are specific or relatively specific inhibitors. This would greatly help in answering important biological and biochemical questions. Initially, Green and his associates²⁰ reported specificity for N-demethylrifampicin and the dimethyl benzyl derivative of rifampicin for the viral enzyme. Unfortunately, N-demethylrifampicin is not a very potent inhibitor^{20,23,48}, but it has in other hands also been somewhat specific for RNA directed DNA synthesis²³. The specificity of the dimethylbenzyl derivative has not been extended. It is, for example, a potent inhibitor of purified DNA polymerases from normal human lymphocytes²³. Some streptovaricins, similar to the findings with N-demethylrifampicin, although not very potent, appear to give a range of some selectivity for RNA directed reactions²³. Ethidium bromide and daunomycin offer little if any specificity. Recently, poly rU was reported to selectively inhibit reverse transcriptase, and it was proposed that it might be used as a rapid and simple approach for differentiating cellular and viral enzymes obtained with crude extracts⁵¹. Although these results have been confirmed⁵², some other viral polymerases were inhibited much less than RLV, and two highly purified DNA polymerases from normal human lymphocytes were inhibited at least as strongly as any viral polymerase⁵², so it is clear that this approach may not be very useful.

Reverse Transcriptase in Cells

Last year an RNA dependent DNA polymerase in some human acute leukaemic cells was described²¹. This was the first report of this activity in a mammalian cell, and it was based on response to both natural and synthetic templates. The response to natural RNA was shown to be RNAase sensitive^{21,48}, resistant to actinomycin⁵³, and sensitive to N-demethylrifampicin^{21,48,53}. Spiegelman and his associates simultaneously found much greater activities with certain synthetic templates with virtually all neoplastic cells compared with normal cells, and proposed a potential prognostic and/or diagnostic use of these templates^{43,54}. Neither of these studies, of course, clarified the origin of these activities, and the point was stressed that, whether viral or cellular, differences in activities between normal and neoplastic cells which potentially might be involved in reversal of information flow could account for variation in RNA species between these cells^{21,49}. It was already known that the DNA polymerase from *E. coli* accepted the synthetic double stranded RNA, poly rA·rU⁵⁵, but no "natural" (cellular or viral) RNA templates were ever included. Subsequently, "RNA" dependent DNA polymerase activities were described in a number of mammalian cells and in leukaemic sera based on the response to synthetic polymeric templates, especially ribohomopolymer·deoxyhomopolymer hybrids (for example, poly dT·poly rA) or DNA^{47,56-58}. As described above, poly dT·poly rA was later shown to lack specificity. Later a DNA polymerase activity from normal cells with a natural RNA (commercial yeast RNA) was reported⁵⁹. This RNA, however, is contaminated with DNA and the response was not shown to be RNAase sensitive; and almost simultaneous with the report on human leukaemic cells, the *E. coli* enzyme was reported to utilize cellular RNA⁶⁰. This reaction was shown to be RNAase sensitive at high RNAase concentrations in the absence of salt. As discussed above, under these conditions double stranded RNA and RNA of RNA-DNA hybrids (as well as single stranded

RNA) will be RNAase sensitive. Thus, in most studies, unequivocal proof of RNA-directed DNA synthesis had not been demonstrated. This is especially true now that it is known that RNA may act as an initiator (primer) for a DNA polymerase since a primer rather than a template may be destroyed by RNAase treatment. Further approaches are needed; and attempts have now been made to look at cells for ribonucleoprotein particulate fractions that carry out endogenous synthesis of DNA, and which are sensitive to RNAase (in conditions that should degrade only single stranded RNA), which allow appropriate product analysis. Activity has been found by Coffin and Temin in non-virus-producing but RSV-transformed rat cells and much less activity in the non-transformed culture cells⁶¹. Preliminary evidence has also been reported of similar particulate fractions in tissue culture in a leukaemic cell line which contained visible viral-like particles⁶², and recently in some fresh human leukaemic blood cells and in chick embryos (P. Sarin, M. G. Sarnagadharan, R. G. Smith, J. Battacharyya and R. C. G., in preparation). As well as RNAase ($10 \mu\text{g ml}^{-1}$; 0.2 M NaCl) sensitivity, the DNA product of an early reaction from the leukaemic pellet was shown to band in Cs_2SO_4 in the RNA region⁶⁴. The conditions of sensitivity to RNAase suggest that if the RNA is only a primer hybridized to DNA it must be very small (fewer than ten nucleotides), yet the Cs_2SO_4 and subsequent velocity gradient analyses indicate that the RNA is large. These results, combined with the previous data, suggest that the reaction in leukaemic cells is RNA directed.

Future Problems

Some of the questions which need early answers are the following. (1) What are the detailed biochemical mechanisms for this enzyme? Are they exactly the same as *E. coli*, always requiring free 3'-OH ends and a primer? (2) What is the nature of the primer in biological situations? Is it RNA, DNA, or both? (3) Are there specific primers for different RNA viruses? (4) Does the enzyme physically differ between type B and type C RNA virus groups? (5) Does the enzyme in viruses from higher forms differ from that of lower animals? (6) Can true *in vitro* replication be accomplished? Are there factors the absence of which gives repair synthesis rather than replication? (7) Are any of the DNA polymerases of neoplastic cells, particularly human, viral in origin (in the absence of whole virus)? (8) Do these or similar cellular polymerases carry out true reversal of information flow in biological situations other than neoplastic transformation? (9) Finally, definitive evidence is still needed to prove a requirement of the viral enzyme for initiation of neoplastic transformation, and more evidence is needed to conclude that it is not required for maintenance of transformation.

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Quasi-stellar Objects and Gravitational Lenses

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The space density of gravitational lens images as a function of redshift is calculated for various cosmological models. One cannot interpret all QSOs as gravitational lens images, unless there is a substantial amount of evolution with z in the sources of the lens images, and also a large fraction of the mass of the universe in the form of compact dark objects.

A conservative estimate, assuming no evolution of the sources, and a smoothed-out density of 7×10^{-31} g/cm³, for the objects which act as lenses, results in a discrepancy by a factor $\sim 10^4$ between the comoving density of lens images and QSOs, out to a redshift of $z \simeq 2.8$.

MANY people have looked into the possibility of observing the gravitational lens effect. Zwicky^{1,2} showed that galaxies offer a much better chance than stars for the observation of this effect, and Barnothy and Barnothy³ have suggested that QSOs may be distance Seyfert galaxies the intensity of which has been enhanced by the gravitational lens mechanism.

Following Refsdal^{4,5} I consider a small source S at a redshift $z = z_s$, and a mass B acting as a gravitational lens at $z = z_b$. The image seen by the observer at O (Fig. 1) consists of two thin crescents which merge into an annular ring when the observer, lens, and source are perfectly aligned. A detailed study of the shape of the lens images has been carried out by Liebes⁶. The important angles involved are: β , angle between lens and source; α , angular separation of images; α_0 , the value of α when $\beta = 0$.

The total amplification, A , is given by

$$A = \frac{1}{2} \left(\frac{\alpha}{\beta} + \frac{\beta}{\alpha} \right) \quad (1a)$$

where

$$\alpha^2 = \alpha_0^2 + \beta^2 \quad (1b)$$

If, before magnification, the source subtends an angle u , then equation (1) is only valid for $\beta \gg u$. For $\beta \lesssim u$ (in which case the

image is an annulus)

$$A \sim \frac{\alpha_0}{u} = A_0$$

If the mass of the lens is M , then

$$\alpha_0^2 = \frac{16 GM H_0}{C^3} \frac{z_s - z_b}{z_s z_b} \frac{1 + z_b}{T(z_s, z_b, \text{model})} \quad (2)$$

$T(z_s, z_b, \text{model})$ is a function of order unity depending on z_s , z_b , and the cosmological model, which has been calculated by Refsdal⁵, G is the gravitational constant, c is the velocity of light and H_0 is Hubble's constant (which we take throughout as 100 km s/Mpc).

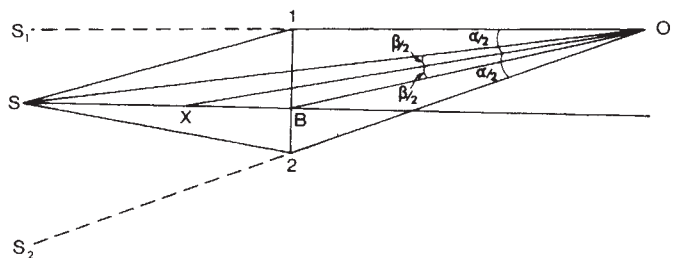


Fig. 1 Diagram showing two light rays S_1O , S_2O from the source S to the observer O which are deflected by the gravitational lens at B . The line XO is a line of symmetry, and S_1 , S_2 are the gravitational lens images.

Fig. 2 shows the amplification as a function of β . For any A_0 and u , the graph of $\frac{A}{A_0}$ against $\frac{\beta}{u}$ is the same shape. A_0 is the maximum amplification and occurs when the source lens and observer are perfectly aligned. Large magnifications are only possible if the unmagnified angular size of the source is small.

Space Density of Lens Images

The probability that a random source in the sky is aligned to within an angle β with a given object is, for small β ,

$$\text{probability} = \frac{\beta^2}{4} \quad (3)$$

If $N(z_s)$ is the number of lenses out to a redshift z when the fraction of objects aligned to within an angle β of a potential lens is

$$\chi(z_s) = \frac{\beta^2}{4} N(z_s) \quad (4)$$

the magnification A is related to β by

From (1a and b)

$$\beta^2 = \frac{\alpha_0^2}{2(A^2 - 1 + A\sqrt{A^2 - 1})} = \frac{\alpha_0^2}{4P(A)} \quad (5)$$

where

$$P(A) = \frac{1}{2}(A^2 - 1 + A\sqrt{A^2 - 1}), A \ll A_0 \quad (6)$$

From (2) we thus have

$$\chi(z_s, A) = \frac{GMH_0}{c^3 P(A)} \frac{z_s - z_b}{z_s z_b} \frac{(1 + z_b) N(z_s)}{T(z_s, z_b, \text{model})} \quad (7)$$

$\chi(z_s, A)$ is the ratio of images (magnified by more than A) to sources, as a function of redshift.

I simplify (7) by taking a mean value of

$$\left\langle \frac{z_b}{z_s} \right\rangle = j = 3/4$$

This is a "round" number which is probably not far from a true average value. The expressions χ and T are insensitive to z_b/z_s .

For small z_s ,

$$N(z_s) \propto z_s^3, \text{ and } T = 1$$

$$\therefore \chi \propto \left(1 + \frac{3}{4} z_s\right) z_s^3 \quad (8)$$

The number of lens images out to redshifts z_s is given for $z_s \ll 1$ by

$$N_L(z_s) \propto z_s^5 \left(1 + \frac{5}{8} z_s\right) \quad (9)$$

Putting $z_b = 3/4 z_s$ in (7) and dropping the suffix s , we obtain for all z

$$\chi = \frac{GMH_0}{3c^3 P(A)} \frac{(1 + 3/4 z)}{z} \frac{N(z)}{T} \quad (10)$$

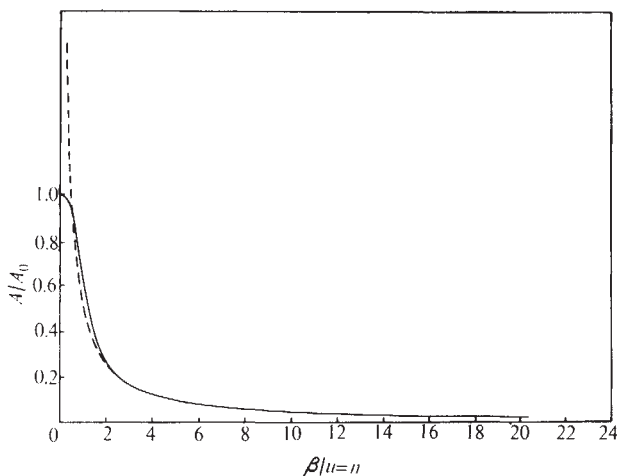


Fig. 2 The ratio of amplification to maximum amplification as a function of $\beta/\alpha_0 = n$. Also shown is the curve $\frac{A}{A_0} = \frac{1}{2n}$ which is a good approximation for $1 < A < 0.9 A_0$.

Galaxies as Gravitational Lenses

I now consider whether extended objects like galaxies can indeed act as effective lenses. For a lens mass of, say, $10^{11} M_\odot$ at a redshift of $z=0.75$ with a source at a redshift $z=1$, the impact distance of the light ray from the centre of the lens is 2.1 kpc ($q_0=1$ model). Because a typical galactic radius is ~ 10 kpc, we must allow for the fact that the light rays pass inside the galaxies.

In this section I work out the effective mass of a galaxy, that is, the equivalent point mass which gives rise to the same deflexion as the galaxy. The effective mass of a galaxy is a function of the impact parameter of the light ray. I take the galaxies to be axially symmetric, and the effective mass $M(r)$, which contributes to the deflexion of the light ray, to be the mass within a cylinder of radius r and axis parallel to the light ray.

For a particular galaxy the impact distance d is the solution of

$$d^2 = \frac{3G}{H_0 c} Y^2 M(d) + \frac{\beta c z' (z_b, \text{model})}{H_0} d \quad (11)$$

where

$$Y = z' (z_b, \text{model}) \left(\frac{1 + 3/4 z_s}{z_s T} \right)^{1/2}$$

and

$$\frac{c z' (z, \text{model})}{H_0}$$

is the ratio of the linear to angular size of a rigid rod at a redshift z . To estimate the typical effectiveness of galaxies as lenses, we consider a source at $z_s=1$ in a $q_0=1$ cosmology. The impact distance d is for $\beta=0$ the solution of

$$d_{\text{kpc}} = 2.12 \left(\frac{M(d)}{10^{11} M_\odot} \right)^{1/2} \quad (12)$$

For any other model, and for any other z value, we solve

$$b d_{\text{kpc}} = 2.12 \left(\frac{M(d)}{10^{11} M_\odot} \right)^{1/2}, \text{ where } b = \frac{0.32}{Y} \quad (13)$$

I take first as a detailed example two models of our own Galaxy due to Innanen⁷ (I include an extra factor of 1.5 in (12) and (13) to correct for random orientation of the Galaxy). For each model we can solve (13) and work out the effective mass of the lens as a function of z_s (Fig. 3).

Table 1 Effective Mass as a Fraction of Total Mass for Different Cosmological Models

Model (see caption to Fig. 3 for notation)	I	E	M	D&S
$M_{\text{eff}}/M_{\text{tot}}$	10%	12%	14%	22%

For the De Sitter and steady state models the effective mass increases with redshift until it equals the total mass; for the three other models the effective mass has a maximum at a particular redshift and then decreases. (This behaviour is related, of course, to the differing z -dependence of angular diameters in the respective models.) In Table 1 the effective mass is expressed as a percentage of the total mass for each cosmological model with $z_s=1$ and averaged for the two Galaxy models.

Taking as a typical example, a source at a redshift $z=1$ and a lens resembling our Galaxy at $z=3/4$ in a $q_0=1$, $\Lambda=0$

model, that angular diameter of the lens image, for perfect alignment is $\alpha_0 = 0.35''$. For magnification factors of ~ 100 to be possible the (unmagnified) angular size of the source must be $\alpha \lesssim 0.0035''$. This corresponds to linear dimensions $\lesssim 25$ pc.

If the source, galaxy and observer are not precisely aligned ($\beta \neq 0$) then the formulae (1) which were derived for a point mass, are only slightly modified, except close to a cutoff point (Fig. 3). The cutoff occurs when the galaxy is not compact enough to act as a gravitational lens, that is, there is no non-trivial solution to (12). If the mass distribution is roughly of the form $M(r) \propto r^2$ then a galaxy can act as a lens with a well defined focal length. This permits the possibility of magnifications far exceeding the values expected from (1). Even for more general conditions, we may substantially underestimate the magnification if we insert M_{eff} (given by the solution of (12) and (13) into (1)). This is because, when source and lens are aligned, the annulus is thicker than for a point mass. For a lens similar to our own Galaxy, this enhances the effective mass by a factor ~ 3 .

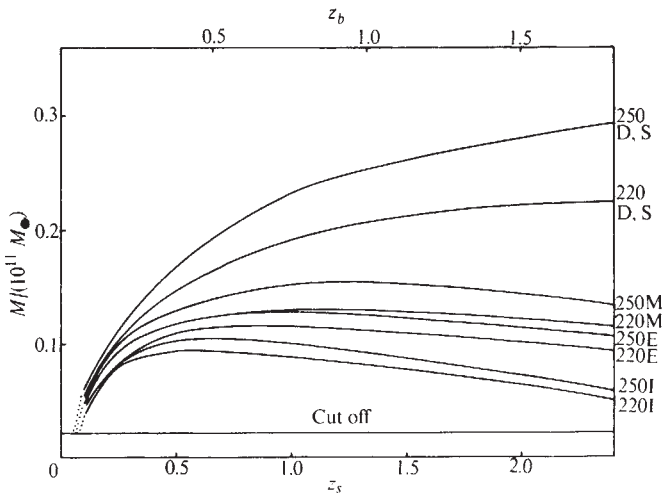


Fig. 3 The effective mass of our Galaxy as a function of redshift. Two models of our Galaxy are used with circular velocity near the Sun of 220 and 250 km s⁻¹. Five cosmological models are used: D, De Sitter; S, steady state; M, Milne; E, Einstein de Sitter; I, $q_0 = 1$, $\Lambda = 0$ model.

Fish⁸ has calculated the effective radius r_e (defined as the radius of a cylinder which includes half the projected luminosity of the galaxy) of twenty-five elliptical galaxies assuming that the galaxy obeys the law⁹

$$\log \frac{B}{B_e} = -3.33 (\alpha_1^{1/4} - 1)$$

Where $\alpha_1 = r/r_e$, B = surface brightness, B_e = surface brightness at $r = r_e$. Assuming a constant mass to light ratio, we find that the average ratio of effective mass to total mass for ellipticals is about 30%. A similar analysis using additional data¹⁰⁻¹³ shows that for spirals this ratio is only of order 1%. We may therefore estimate, very roughly, that the mean value of effective mass to total mass (where galaxies are weighted according to their space density and total mass) is $\sim 25\%$. De Silva^{14,15} has obtained similar results, although he assumed a different form of mass distribution in the galaxies.

Luminosity Functions

A_0 is the maximum magnification of the lens when $\beta = 0$. Thus the lens images arising from magnification of sources with a given luminosity F_0 would have an apparent "cumulative

luminosity function" (CLF) $Q(F) \propto F^{-2}$ (for $\frac{F}{F_0} \lesssim 0.9A_0$). This compares with the results $Q(F) \propto F^{-1.19}$ and $Q(F) \propto F^{-1.6}$ obtained by Schmidt^{16,19} (Fig. 4).

If $\phi_s(E) dE$ is the number of sources with luminosity E to $E + dE$, and $\Phi_Q(F) dF$ is the corresponding function for lens images, then

$$\Phi_Q(F) dF = \left(\int_x \phi_s(F/x) \frac{p(X)}{x} dx \right) dF$$

where $p(X)$ is the probability of a source magnification being X to $X + dX$.

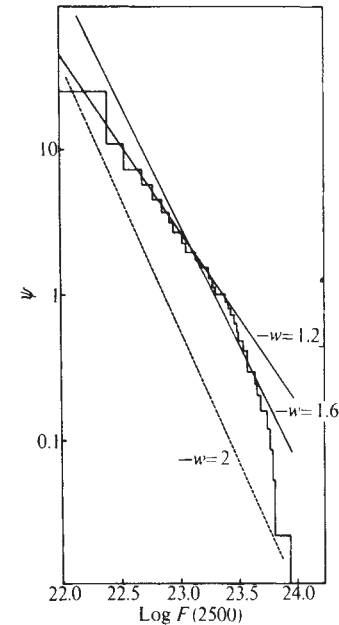


Fig. 4 The cumulative luminosity function for lens images and QSOs at a given redshift. The lens images have a logarithmic slope $-w=2$. Shown are two curves for QSOs having logarithmic slopes at the low luminosity end of $-w=1.2$ and 1.6 .

If the CLF of the sources has a logarithmic slope flatter than $1/E^2$ then the CLF for the lens images will still be $1/F^2$. It is only if the CLF for the sources is steeper than $1/E^2$ that the lens images have the same CLF as the sources.

Number of Lens Images

The CLF of QSOs is poorly determined observationally, and a law $Q(F) \propto F^{-2}$ is not inconsistent with the data given here. We therefore consider under what circumstances it is possible to interpret all QSOs as gravitational lens images.

As a rough estimate of the co-moving density of QSOs with $\log F(2,500) \geq 22.0$, at $z \approx 2.8$, I take 1.2×10^{-5} Mpc⁻³, which is derived from numbers quoted by Lynden-Bell and Schmidt (unpublished). They refer to QSOs above a certain threshold of radio intensity, so the estimate may be too low by an order of magnitude. In view of the great uncertainty, however, it can be adopted in the following calculations. The present density of Seyferts with $10^{20} \lesssim F \lesssim 10^{21}$ is¹⁷ $\sim 3 \times 10^{-4}$ Mpc⁻³ and the present density of N-type galaxies with $10^{21} \lesssim F \lesssim 10^{22}$ is $\sim 3 \times 10^{-6}$ Mpc⁻³. If we make the conservative assumption that Seyferts and N-galaxies have the same density (per co-moving volume) at all epochs, and that there are no effective lenses apart from elliptical galaxies, then we find from (7) that the number of lens images out to $Z = 2.8$ falls short of Lynden-Bell and Schmidt's estimate by a factor of $\sim 10^4$ for a $q_0 = 1$, $\Lambda = 0$

model and $\sim 2 \times 10^3$ for a $q_0 = \frac{1}{2}$, $\Lambda = 0$ model. Thus on this ultra-conservative hypothesis, it is unlikely that even one of the known QSOs can be interpreted in this way. The number of lens images would obviously be enhanced if a large amount of additional matter existed in the form of "dark objects" sufficiently compact to act as effective lenses. Even if the smoothed-out present density of such objects amounted to $4 \times 10^{-29} \text{ g cm}^{-3}$ (corresponding to the overall mean density of a Friedmann model with $q_0 = 1$), we would still only be able to account for $\sim 0.3\%$ of all QSOs as lens images. (This number is rather uncertain and may be as high as 1% or 2%. But, even if this were the case, then in order to explain all QSOs as lens images we still need evolution in the sources.)

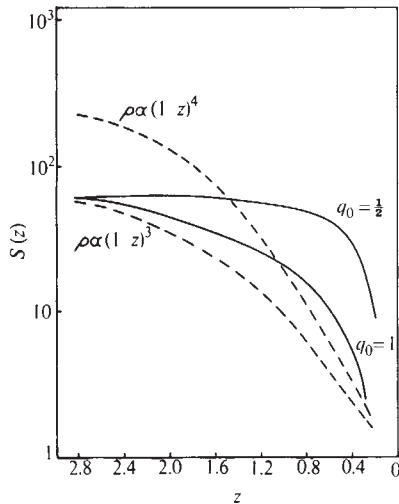


Fig. 5 Co-moving density of sources (Seyfert and N-galaxies) $S(z)$ as a function of redshift for two cosmological models assuming all QSOs are lens images. Also shown are evolution laws $\rho \propto (1+z)^3$ and $\rho \propto (1+z)^4$. There is a large uncertainty in the normalization of the curves.

This result can be deduced from the work of Refsdal¹⁸, who has calculated the apparent-luminosity distribution of distant light sources in a universe where all the material is concentrated in point masses. He finds, in effect, that the CLF for the images must, at all redshifts, be below the line $\psi_L \propto \frac{1}{F^2}$ (where F is the luminosity) extrapolated from the unmagnified luminosity function of the sources. This condition would be violated if the QSOs at large redshifts were all lens images of Seyfert and N-galaxies, and the latter had the same coordinate density as at the present epoch. Refsdal's analysis includes the more general case when the apparent luminosity is affected by several masses close to the line of sight¹⁹⁻²².

The numbers quoted for the density of Seyfert, N-galaxies and QSOs are not very well determined, but in order that Refsdal's condition is not violated, there must be an evolution in the co-moving density of Seyfert and N-galaxies, by a factor S , of at least 50-300 from $z=0$ to $z=2.8$, together with at least half of the density of the universe ($q_0=1$ model) that is $2 \times 10^{-29} \text{ g cm}^{-3}$ in the form of dark compact objects, in order that the expected number of lens images corresponds to the number of QSOs out to a redshift $z=2.8$.

An even larger factor for the evolution of Seyfert and N-galaxies would allow a proportionally smaller smoothed out density of objects which act as lenses.

In Fig. 5 I plot, using (10), the relative co-moving density $S(z)$ as a function of redshift for Seyferts and N-galaxies based on two cosmological models, assuming that all QSOs are lens images. The normalization is rather uncertain. Even without

evolution in the sources, the lens images evolve quite rapidly (see (8)). Hence, when we introduce evolution of the sources, and assume all lens images are QSOs, we obtain a rapid increase in the density of sources from $z=0$ to $z=0.4$ together with a slow increase for $z>0.4$ which can be seen in Fig. 5.

Properties of Lens Images

If the lenses are predominantly "dark objects", and not ordinary galaxies (as must be the case if the lens effect is to be astronomically significant), then in order that the appearance of the lens images be starlike the masses of these objects cannot be too great. For $z_s=1$, $M_{\text{eff}} < 2 \times 10^{11} M_\odot$; and for $z_s=0.2$, $M_{\text{eff}} < 16 \times 10^{11} M_\odot$.

I have assumed when working out the luminosity function that $A \ll A_0$. The value of A_0 is given by $A_0 = \alpha_0/u$. Assuming a constant α_0 and that the Seyfert nuclei have a standard size, then $\frac{u=H_0 d}{z'}$ where d is the radius of the Seyfert nuclei, $z'=z'$ (z , model). For small z , $z'=z$.

Thus

$$A_0 = \frac{\alpha_0 c z'}{H_0 d}$$

So as we go out to a larger redshift A_0 increases. The line emitting region in Seyfert and N-galaxies is larger than the continuum region, thus when there is a high magnification and the source lens and observer are well lined up, the continuum region will be magnified more than the line region.

Taking an example of our Galaxy at $z=3/4$ and a source at $z=1$, if we define:

$$A_1 = \frac{2,500}{r_{\text{pc}}}$$

where r_{pc} is the radius of the line emitting region, then the continuum to line ratio will be higher for lens images which result from magnifications greater than $\sim A_1$.

For $r_{\text{pc}} \sim 100 \text{ pc}$, $A_1 \sim 25$, and the high luminosity tail of the lens images

$$\left(\frac{F}{F_0} \gtrsim 25 \right)$$

would all have their continuum enhanced relative to their line emission.

The luminosity function for sources and lens images cannot be a continuous function but must exhibit a break between the two populations. If most QSOs are lens images then the luminosity function should show a distinct upward trend in going from QSOs to N-galaxies. There is some evidence for such a situation (D. Lynden-Bell, unpublished work). The break becomes less marked for higher redshifts.

Another difficulty in interpreting QSOs as gravitational lens images is to explain extended radio features. An extended source cannot be magnified, and any extended radio components of QSOs have to be attributed to either the lens galaxy or the source. The Seyfert galaxies in general do not show many radio features, and none of the observed ones has the double radio source structure that so many QSOs exhibit. I have, however, shown that the N-galaxies make a significant contribution as sources of gravitational lenses, and many of them do show double radio source structure.

This might provide an explanation why the radio, N-galaxies, and QSOs which exhibit double radio source structure all seem to follow a natural sequence²³.

If the lens or object has a proper motion then the amplification will change with time. Typically, however, the time scale for a change of 0.1 mag is $\sim 10^3 \text{ yr}$. The Earth's motion around the Sun will result in a change of only about 10^{-5} mag over the year.

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Reconstruction of the South-West Pacific Margin of Gondwanaland

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New Zealand and the surrounding regions of the South-West Pacific have undergone a complex tectonic development since the break-up of Gondwanaland began in the Mesozoic. In this article, data relevant to reassembly of the continental fragments in the South-West Pacific are examined and a fairly detailed reconstruction is proposed as a basis for further discussion.

PREVIOUS reconstructions have been made of the Australia–Antarctica fit^{1–3} and, following recognition of the transcurrent nature of the Alpine Fault⁴, geological interpretations of the New Zealand area have been proposed^{1,5,6}. Regional reconstructions on a larger scale have also been attempted^{1,7–12}, but these have failed to make full use of bathymetric, geophysical, geological and tectonic relationships. In some cases^{9–11} large faults and displacements have been postulated for which there is no geological evidence.

The starting point for the reconstruction presented in this article is the fit of Australia and Antarctica, which has been independently computed using the 1,000 fathom line² and the 500 fathom line³. These fits are essentially identical and require that the Australian and Antarctic plates be moved back together along lines parallel to the observed transform faults. Geological data from the Antarctic coast seem to support this reconstruction and it is unlikely to require extensive modification.

The remaining fragments of the old Gondwana continental crust have to be defined before refitting them against Australia–Antarctica. I have done this by interpretation of bathymetric maps, aided by available data on crustal thickness deduced from seismic refraction profiles and geological data. Fig. 1 is a

compilation of bathymetric data and in Fig. 2 I have delineated the continental areas as discussed below and sketched the geology and the plate boundaries that are at present active.

In drawing the boundary of an area of continental crust, the relationship between crustal thickness and bathymetry is the chief consideration. When a continental block breaks apart, “necking” occurs between the fragments until, ultimately, new oceanic crust begins to form between them^{13,14}. The edge of the continental block is then a transition zone from continental crust (25 to 50 km thick) to oceanic crust (5 km thick) and the boundary of the block must be drawn within this zone. In the case where the block is above sea level, this level is taken as the edge of the continental shelf using the 1,000 m line. Where the continental slope is steep, the contours are closely spaced and a reasonably precise delineation of the block is thus possible. In the case of submerged areas with relatively gentle slopes the edge of the block cannot be so closely defined.

The edge of the Australian–Antarctic block is drawn at the 1,000 m contour. The continental slope is steep except in the Coral Sea region (Fig. 1) where extensive reefs and seamounts complicate the bathymetry. Recent refraction profiles¹⁵ have shown that the Queensland Plateau is underlain by continental crust and the 2,000 m line is used here to include it as part of the Australian block.

New Zealand is only a small part of an extensive submarine plateau (Fig. 1). To the south and east, the Campbell Plateau and Chatham Rise are underlain by continental crust¹⁶. Typically “continental” rocks outcrop on the islands on these plateaux and these have strong affinities to New Zealand rocks, suggesting that the plateaux are offshore extensions of New Zealand^{6,8}. The 2,000 m contour is used here to delineate the edge of the New Zealand block.

Two broad submarine ridges extend north-west from New Zealand. Recent work¹⁷ confirms earlier views¹⁸ that both the Lord Howe Rise and Norfolk Ridge are comprised of crust of continental character. The Norfolk Ridge continues to New Caledonia, which is closely related geologically to New

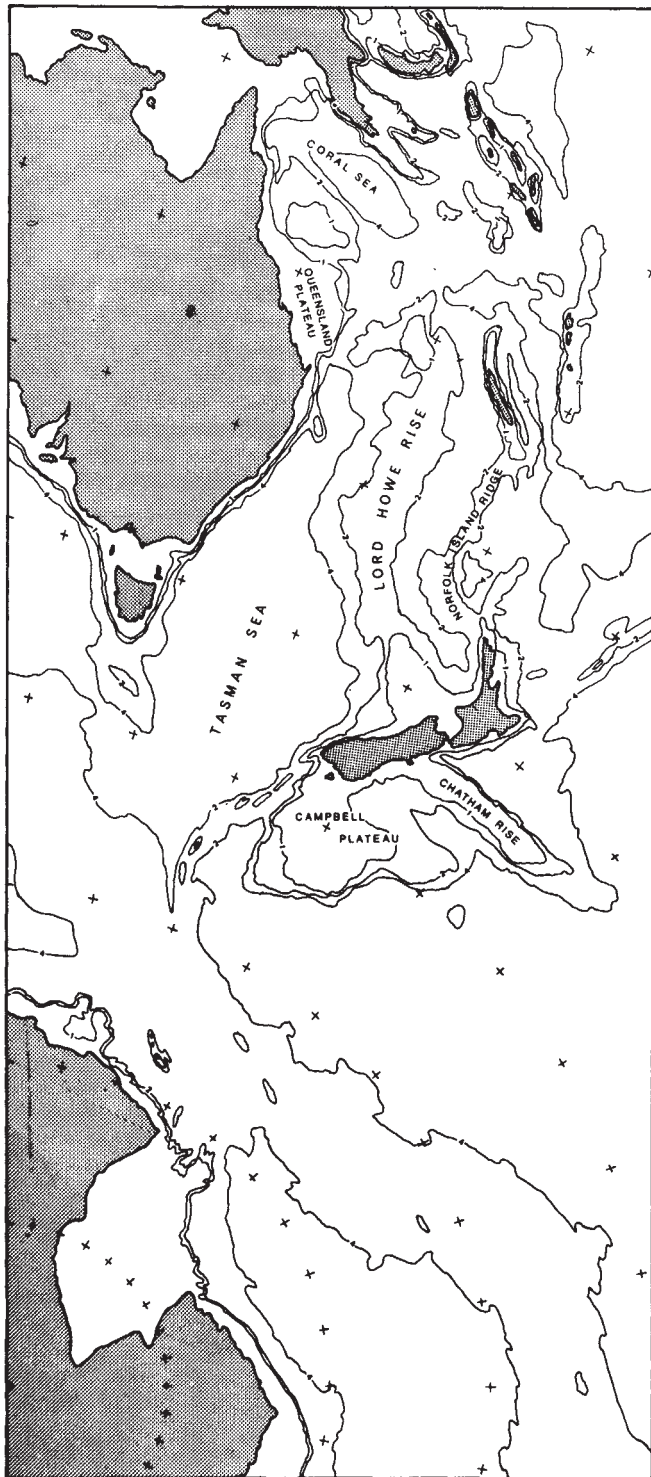


Fig. 1 Bathymetric map of the South-West Pacific, showing 1, 2 and 4 km submarine contours. (Based on a composite projection. ×, 10° intersections.)

Zealand¹⁹. This ridge probably represents the eastern margin of Gondwanaland before break-up, for the ridges and islands to the east are all much younger. The "edge" of the Lord Howe Rise and Norfolk Ridge is difficult to define accurately, as they both have gentle slopes, and is here taken at the 2,000 m line (Fig. 2). The Tasman Sea is underlain by oceanic crust^{17,18} and the crust in the New Caledonia Basin is much thinner than on the flanking ridges¹⁷.

The Louisiade Ridge, an offshore continuation of New Guinea, also has continental characteristics¹⁵. Reefs in the area

complicate the bathymetry but parts of the Louisiade and Rennell Ridges are probably fragments of continental crust. The limits of this crust cannot be drawn with certainty and are only sketched in the reconstruction.

Finally, part of the Solomon Islands may be a fragment of continental crust. Officer¹⁸ suggests a crustal thickness of 15 km and the occurrence of a probable Cretaceous igneous and metamorphic basal complex²⁰ indicates that part of the Solomon Islands may be a fragment of the outer edge of the Papuan Geosyncline.

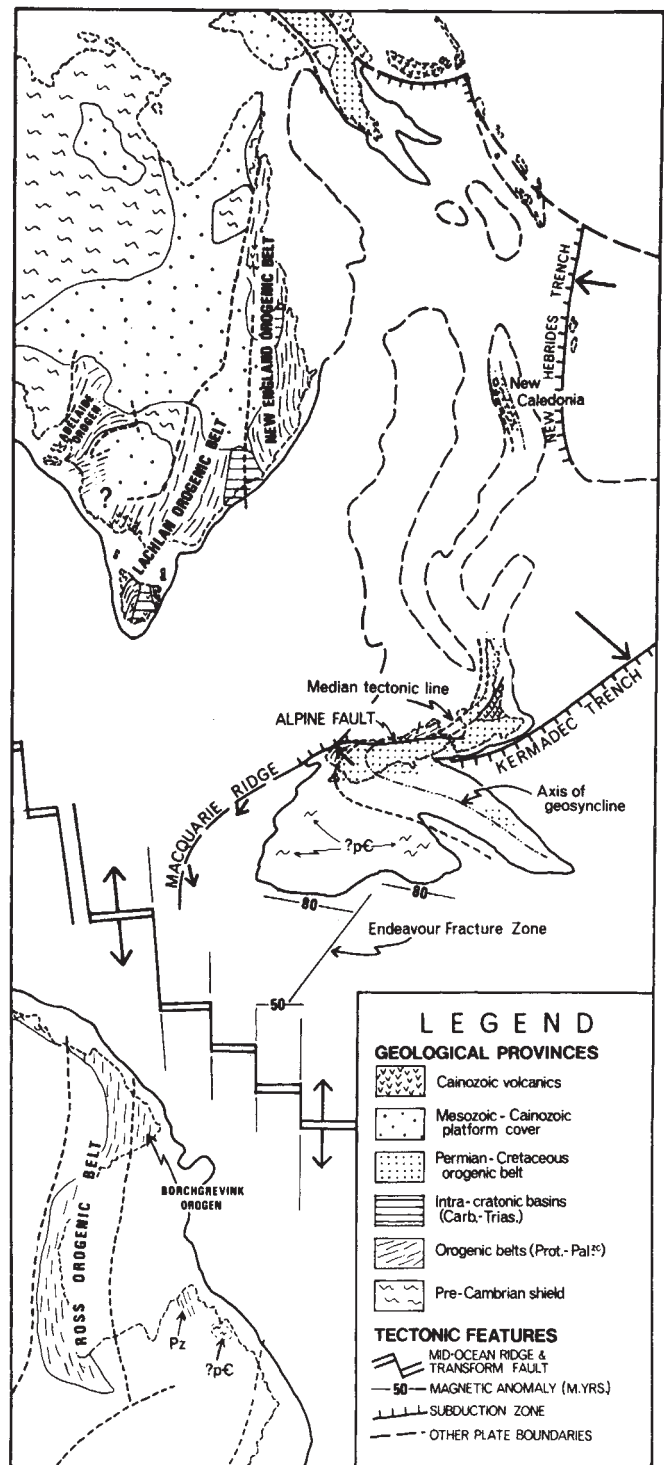


Fig. 2 Geology and recent tectonics of the South-West Pacific. Areas of continental crust are bounded by solid and dashed (where less precise) lines. (Same projection as Fig. 1.)

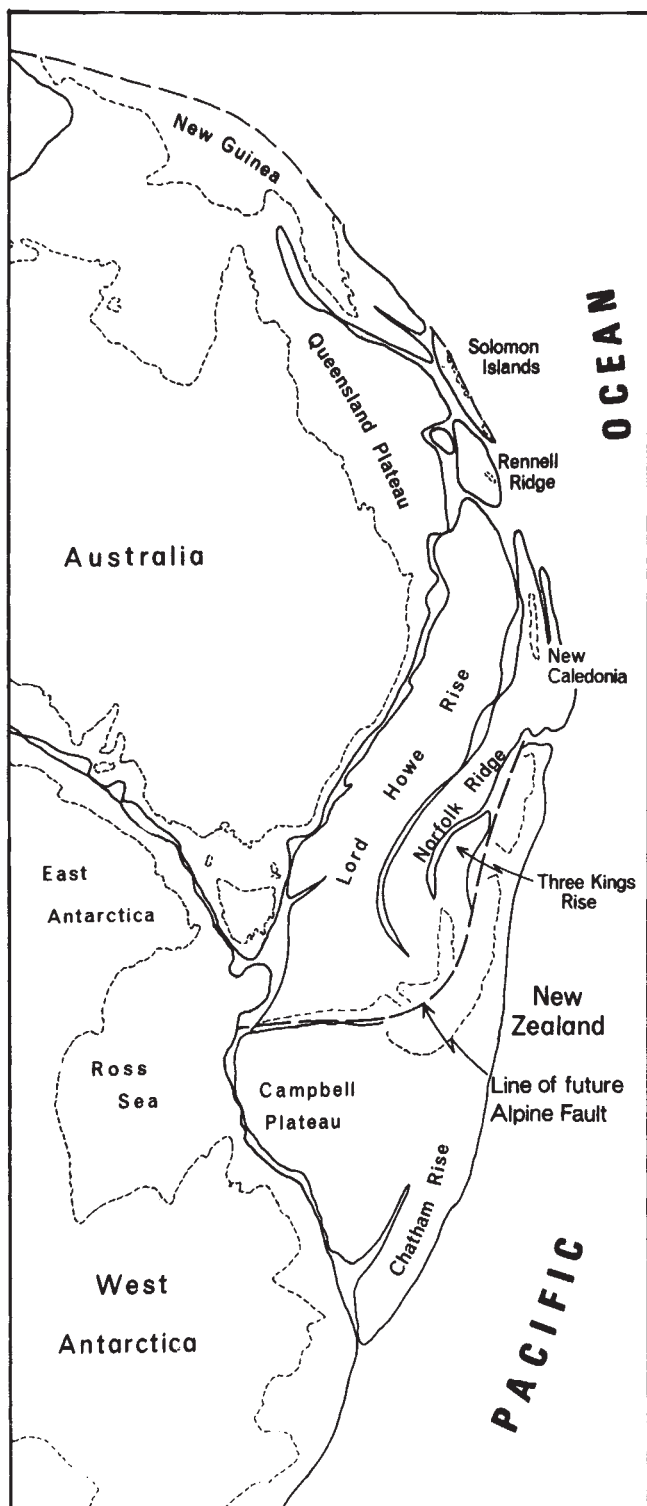


Fig. 3 Morphological reconstruction of the South-West Pacific margin of Gondwanaland. Present topographic names given for reference.

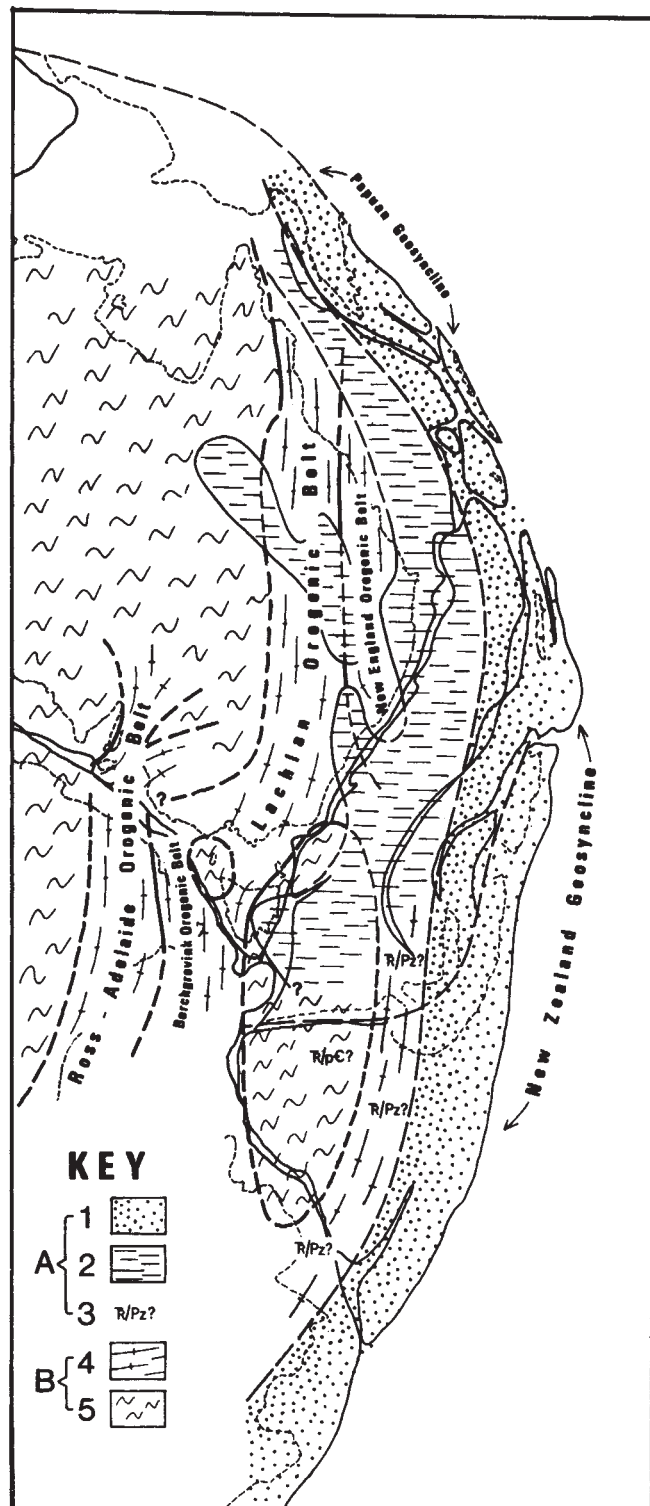


Fig. 4 Triassic palaeotectonic map superimposed on Fig. 3. A, Areas of Triassic deposition: 1, Geosynclinal sediments along Pacific margin; 2, platform and intracratonic basin sediments in eastern Australia; 3, inferred platform sediments on Palaeozoic (Pz) and Precambrian (pC) basement in New Zealand and Antarctica. B, Stabilized continental crust: 4, Late Proterozoic and Palaeozoic orogenic belts (see text); 5, Precambrian shield.

Reassembly of Fragments

The geological and tectonic features which provide a framework for the reconstruction are shown in Fig. 2 and the Australia–Antarctic fit^{1–3} is the basis of the reassembly. The next stage is the closure of the Southern Ocean between New Zealand and Antarctica. Marine magnetic profiling results indicate that the Pacific–Antarctic Ridge formed between the Campbell Plateau and West Antarctica during the late Cretaceous (80 m.y. BP, ref. 21) and that a great change in spreading direction occurred in the early Eocene (50 m.y., ref. 22). Reversal of separation to 50 m.y. BP brings the Campbell Plateau and West Antarctica closer together. It has been shown that the spreading rate from 50 to 80 m.y. BP increased eastwards across the Endeavour Fracture Zone²² and reversal of this motion leads to a relative clockwise rotation of the Campbell Plateau to bring it up against West Antarctica. The morphological fit between these blocks seems to be very good and could probably be tested by mathematical analysis. The Chatham Rise is then laid back against the Campbell Plateau, closing the Bounty Trough and completing this part of the reassembly (Fig. 3).

South of the Queensland Plateau the northern end of the Lord Howe Rise is close to the Australian block. The Tasman Sea seems to have opened as a sphenochasm¹ and there is no evidence for north–south transcurrent displacements at its northern end. The Lord Howe Rise can, therefore, be replaced directly against Australia, thus closing the Tasman Sea (Fig. 3). Precise morphological correspondence cannot be demonstrated because of the poor definition of the Lord Howe Rise.

A large displacement between the Campbell Plateau and the southern end of the Lord Howe Rise is required to close the Tasman Sea completely. This displacement is identified with the Alpine Fault of New Zealand (Fig. 3). The amount of lateral displacement required to complete the morphological fit is equal to the observed transcurrent movement on the Alpine Fault and thus, in the reconstruction, pre-drift New Zealand assumes the configuration postulated by previous workers^{1,5,6}. But the only important internal deformation in any of the blocks in this reconstruction is along the Alpine Fault zone through New Zealand and the length of the Lord Howe Rise is just sufficient to fit in the available space between the Queensland and Campbell Plateaux.

The Norfolk Ridge is laid back against the Lord Howe Rise (Fig. 3), closing the New Caledonia Basin. The projection of the Alpine Fault through North Island, New Zealand²³, is used to bring the eastern part of North Island towards the Three Kings Rise, and this completes the continuity of the New Zealand Geosyncline (Fig. 4).

Finally, the Coral Sea sphenochasm is closed, thus bringing eastern New Guinea against the Queensland Plateau; the remaining continental fragments are fitted into the gap between New Guinea and New Caledonia (Fig. 3).

This reconstruction does not require new transcurrent faults to be postulated and maintains internal stability within the continental blocks; only seafloor spreading and the formation of new ocean basins are needed to achieve the present configuration.

Geological Considerations

The regional geology is summarized in Fig. 2 and three divisions can be recognized: (a) Precambrian basement rocks; (b) late Precambrian and Palaeozoic orogenic belts, and (c) Mesozoic and Tertiary orogenic belts.

Precambrian basement rocks form the nucleus of Australia and East Antarctica and generally comprise high-grade metamorphics, crystalline intrusives and extrusives and some areas of relatively undisturbed sediments, which together form the “foreland” to the succeeding events. The eastern part of Australia has experienced a complex sequence of events which is only understood in principle at present. Further work is in progress on the interpretation of this area (Solomon and

Griffiths, unpublished results) and only the outline will be considered in this article.

In eastern Australia, two late Precambrian to Palaeozoic deformed belts are recognized—the Adelaide and Tasman Geosynclines. The continued use of the term geosyncline in this context is inappropriate (Solomon and Griffiths, unpublished results) and instead we refer to the Adelaide Orogenic Belt and the Tasman Orogenic Zone. The Tasman Orogenic Zone is further divided into two units, the Lachlan and New England Orogenic Belts. The present position of these belts is shown in Fig. 2, and their position on the reconstruction is indicated in Fig. 4.

The Adelaide Orogen in South Australia is composed of a thick Proterozoic to Cambrian sedimentary sequence, which underwent high level paratectonic²⁴ deformation during the Lower Ordovician. In Antarctica the Ross Orogen shows a parallel development, with Proterozoic to Cambrian sedimentation followed by late Cambrian–Ordovician deformation²⁵, and these two belts are aligned in the reconstruction.

The Lachlan Orogen is composed of deformed Cambrian to Devonian sediments. It is internally complex and Cambrian to Devonian orthotectonic and Ordovician to Devonian paratectonic sequences are recognized. An important orogenic event occurred in the mid-Devonian. The Lachlan Orogen continues into Antarctica as the Borchgrevink Orogen in northern Victoria Land²⁵, where the metamorphosed Cambrian Robertson Bay Group has an unfaulked strip of Silurian (?) to Devonian Bowers Group sediments²⁶. The whole orogen was intruded by granites and stabilized as continental crust by the late Devonian.

Sequences similar in age and variety of deformational style occur in North-West Nelson and Fiordland, New Zealand, where a Cambrian to Devonian orthotectonic unit and an Ordovician to Devonian paratectonic sequence are recognized (my unpublished results).

To the west of the Alpine Fault and to the south of these Lachlan sediments, probable Precambrian rocks occur²⁷ and I suggest that a large Precambrian block was present within the Lachlan Orogen (Fig. 4). Precambrian rocks form a basement to Lachlan sediments in Tasmania and possible Precambrian rocks occur in Marie Byrd Land, West Antarctica²⁵ (Fig. 2); this Precambrian block is, therefore, tentatively drawn as in Fig. 4. The rocks exposed in North-West Tasmania are considered to be part of a smaller Precambrian block (Fig. 4).

The New England Orogen is a Silurian to Permian belt which is also internally complex; its outcrop is confined to eastern Australia at present (Fig. 4). The last stages of granite intrusion in the New England Orogen, in the Permian, completed the stabilization of the Palaeozoic margin of Gondwanaland as continental crust. Thereafter until the mid-Jurassic sedimentation continued along the Pacific margin, forming the Papuan and New Zealand Geosynclines (Fig. 4). This geosynclinal belt underwent orogenesis from mid-Jurassic to mid-Cretaceous; the continent then began to break apart; the fragments attained their present configuration during the Tertiary as seafloor spreading occurred (Griffiths and Varne, in preparation).

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Cholinergic Receptor Molecules and Cholinesterase Molecules at Mouse Skeletal Muscle Junctions

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Studies of the binding of labelled α -bungarotoxin to mouse skeletal muscle endplates have allowed the quantification of acetylcholine receptor sites at the post-synaptic membrane.

THE molecules of acetylcholinesterase (AChE) at individual motor endplates in various vertebrate skeletal muscles have been enumerated^{1,2}, and in mouse muscle endplates^{3,4} they have been located principally or entirely at the post-synaptic membrane. The methods used^{1,2,5} rely on reaction of AChE with radioactive diisopropylfluorophosphate (DFP) (with appropriate chemical devices for specificity) and cellular autoradiography. We report here the next step in the analysis of functional components at the motor endplate, that is, the counting *in situ* of the molecules of the cholinergic receptor.

For this purpose, an agent is required that binds irreversibly and with high specificity to the cholinergic receptor. There is extensive evidence⁶⁻⁹ that α -bungarotoxin, isolated from the venom of the snake *Bungarus multicinctus*, has the desired properties. We have, therefore, labelled α -bungarotoxin with tritium to high specific activity, for reaction at mammalian motor endplates and quantitative autoradiography.

Labelling of Receptors

B. multicinctus venom was fractionated¹⁰ on 'CM-Sephadex C-50': the α -bungarotoxin was eluted in the second of the nine protein peaks separated. Two chromatographic separations on CM-cellulose (Whatman CM-52) in 0.05 M ammonium acetate (pH 5.8) yielded a peak of pure α -bungarotoxin.

Labelling was by reaction¹¹ with ³H-acetic anhydride, with isolation by two gel filtrations on 'G-25'. The product (³H- α -bungarotoxin) contained radioactivity corresponding, in three preparations, to 0.40 to 0.80 acetyl groups per toxin molecule, and had an LD₅₀ in mice and a blocking potency on the rat phrenic-diaphragm preparation⁶ equal to those of the pure unlabelled toxin.

After lethal injection of ³H- α -bungarotoxin into mice, autoradiographs prepared¹ from striated muscle sections showed a clear cut and specific labelling of all endplates (Fig. 1). To

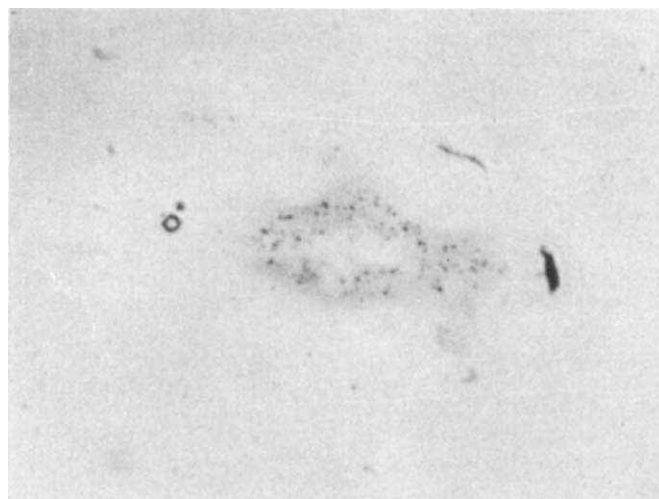


Fig. 1 Autoradiograph (18 days exposure) of diaphragm labelled with ³H- α -bungarotoxin, showing a single endplate (seen by light staining¹² for AChE, performed through the developed stripping film). Note that outside the endplate area, labelling is at background level only.

phrenic nerve-diaphragm preparations from male mice (17–20 g), ^3H - α -bungarotoxin ($10\ \mu\text{g ml}^{-1}$) was applied in gassed Tyrode solution at 37°C , with recording of isometric twitch tension on a Grass 5D polygraph. The twitch and tetanic responses both declined to zero over about 12 min (Fig. 2, curve *a*). After various reaction times, 10^{-5} M *d*-tubocurarine washes were given, followed by Tyrode washes and autoradiography¹. Such *d*-tubocurarine treatment was shown to protect effectively from the ^3H - α -bungarotoxin reaction, confirming the evidence^{6,7,9} for the specificity. Repeated washes of portions of a labelled muscle with Tyrode did not reduce the final mean grain density, confirming irreversibility. A saturating value for the mean grain density at the endplates was reached after 20–30 min total reaction, that is, later than the disappearance of response (Fig. 2, curve *b*). This maximum uptake value was shown to be the same as that reached after paralysis *in vivo* by excess ^3H - α -bungarotoxin (Table 1).

sites at each endplate (Table 1) was equal to the number of ChE active centres in these two mouse muscles. Evidence that this equality may be general was obtained by using muscles from a remotely related species, the chicken (Table 1), and by approximately similar results in single experiments on rat sternomastoid and rhesus monkey diaphragm. In eel electric tissue isolated membranes, the same equality of the sites has been deduced^{9,15}.

The number of labelled toxin-binding sites per endplate was not changed by pre-treatment with DFP to saturation of the ChE sites, nor did saturation with the toxin decrease the ^3H -DFP labelling. Hence the two types of active centres at the endplate are distinct and independent.

Waser and co-workers^{16,17} have estimated the cholinergic receptor active centres in the mouse diaphragm endplate to be about eight times less than our value. The ^{14}C -labelled curariform drugs they used bind reversibly and are readily

Table 1 Grain Densities over Toxin-labelled and DFP-labelled Endplates

Animal	Muscle	Mean grains $\pm$ s.e. per field Toxin label	Mean grains $\pm$ s.e. per field DFP label	Ratio of sites Toxin: DFP	Receptors per endplate*
Mouse 1	Diaphragm (D)	11.9 ± 0.3 (208)	26.6 ± 0.5 (184)	1.14	
2	Diaphragm	11.8 ± 0.3 (164)	33.8 ± 0.5 (170)	0.89	
3	Diaphragm	10.0 ± 0.3 (155)	14.0 ± 0.4 (190)	1.00	
4	Diaphragm	14.1 ± 0.2 (274)	21.0 ± 0.4 (186)	1.13	
5, 6	Diaphragm	14.3 ± 0.4 (109) 13.9 ± 0.3 (109)	22.2 ± 0.4 (163)	1.09	
5, 6	Sternomastoid (S)	15.7 ± 0.4 (145) 15.6 ± 0.4 (145)	28.9 ± 0.4 (148)	0.92	
Mouse (mean)				1.02	(D) 3.0×10^7 (S) 8.7×10^7
Chicken 1	Post. latiss. dorsi	11.8 ± 0.3 (160)	16.0 ± 0.2 (251)	1.01	$3\text{--}5 \times 10^7$
2	Biventer	11.6 ± 0.4 (86)	14.6 ± 0.4 (165)	1.09	

Labelling was *in vitro*, with ^3H - α -bungarotoxin at $10\ \mu\text{g ml}^{-1}$, 37°C , 45 min; except that mouse 5 was killed by a five-fold supra-lethal dose of ^3H - α -bungarotoxin and its muscles were autoradiographed with (upper line) or without (lower line) a further exposure to ^3H - α -bungarotoxin *in vitro*. The ^3H -DFP labelling, in that case only, was performed on muscles from another animal (6), autoradiographed on the same slides. Specific activity (Ci mmol^{-1}) of ^3H -DFP was 3.24, and of ^3H - α -bungarotoxin preparations was from 1.26 to 2.32. Number of labelled endplate fields ($6\ \mu\text{m} \times 6\ \mu\text{m}$) shown in parentheses. Chicken data obtained by Dr J. Jedrzejczyk.

* Number of α -bungarotoxin binding sites per endplate, taken (since the ratio is 1.0) as the absolute number of the DFP-reactive sites per endplate, measured^{1,2} by β -track counting of micro-dissected fibres from ^{32}P -DFP-labelled muscles, from four to six animals in each case. For chicken muscles, range arises from different ages and hence fibre sizes.

Structures which were well labelled with ^3H - α -bungarotoxin but showed no staining¹² for ChE in our (minimal) conditions of incubation were occasionally encountered and were tentatively identified as motor spindles. These were not included in the counts reported, but they suggest that the receptors are not necessarily associated with AChE sites.

Comparison with Cholinesterase Molecules

At saturation, the mean density of ^3H - α -bungarotoxin labelled sites at the endplates was compared with the mean density of endplate sites labelled to saturation^{1,2} with ^3H -DFP in parallel preparations from the same muscles (Table 1), yielding (with the specific radioactivities used) the ratio of these two types of site at the endplate. The endplate sites that react rapidly with DFP include AChE^{1,2}, but in addition comprise other cholinesterases^{2,13,14}. We have now found by the autoradiographic method that 95% or more of the DFP-reactive sites at the endplates measured could be protected from ^3H -DFP (10^{-5} M , 22° , 30 min) reaction by the presence of 10^{-5} M eserine. We therefore take the total ^3H -DFP labelling at endplates (Table 1) as representing essentially the cholinesterase active centres (ChE) of all types (including AChE). Hence, the absolute number of α -bungarotoxin binding receptor

washed out, and autoradiographs at the single endplate level were not obtained in that method^{16,17}; we believe that these factors led to an underestimate of the total of cholinergic receptor sites at this synapse.

Molecular Requirements for Transmission

The time-course of the inhibition of transmission (Fig. 2, curve *a*) was distinctly different from the time-course of the binding of the toxin seen at the endplates. A curve relating receptor occupancy to response blockade was constructed thus, and was confirmed by measurements of the uptake at endplates made by autoradiography of some individual recorded preparations (Fig. 3). The results of Fig. 3 agree qualitatively with those obtained¹⁸ less directly by a dose-ratio analysis of effects of reversible antagonists and stimulants on two cat muscles. By our method, all the fibres still responded when, on the average, 45% of the receptor sites were blocked. The steep rise in inhibition is centred at 70% receptor blockade and this mid-point is attributed to the depression of the endplate potential to the threshold of the muscle action potential in the average of the population of fibres. That threshold is close to 35 mV above the resting potential, while the total range of depolarization that release of transmitter can produce

at the unblocked endplate is about 75 mV above the resting potential^{19,20}. The data suggest, therefore, that if there are spare receptors, that is, receptors that can be irreversibly blocked without decreasing the maximum (75 mV) depolarizing effect of the normally released transmitter, these must be less than one-half of the total present. Definition of the precise course of the response as the receptors become occupied will be possible by a combination of the autoradiographic technique with intracellular electrical recording methods. Already, however, the data of Figs. 2 and 3 exclude the case that there is a substantial reserve of receptors at the endplate.

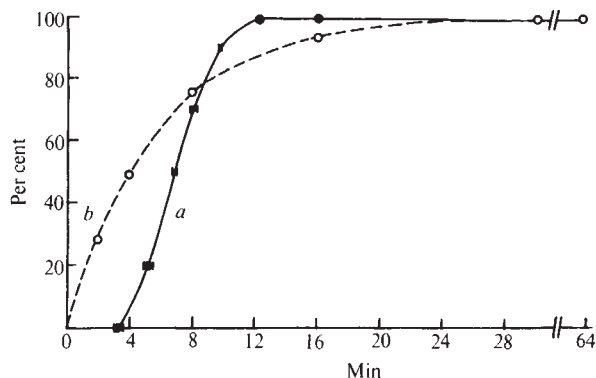


Fig. 2 Reaction of diaphragm endplate *in vitro* with ³H- α -bungarotoxin (10 μ g ml.⁻¹, 37°C). *a*, Inhibition (%) of twitch or tetanic (120 stimuli s⁻¹) response. Mean $\pm$ s.d. of the preparations from ten mice shown (s.d. omitted for values at 100%). *b*, Endplate labelling (each point is the mean for 100–200 fields over endplates), expressed as a percentage of the maximum. Preparations from two mice each gave the same curve.

gether correspond (if all are in the post-synaptic membrane) to a high density, about one subunit per 5000 Å². The simplest model compatible with all the data involves a mosaic of receptors and ChE over the whole post-synaptic membrane.

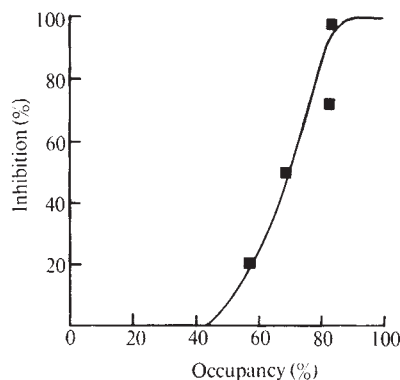


Fig. 3 Curve relating the percentage inhibition of response to the percentage of the ³H- α -bungarotoxin-binding sites occupied. The curve was constructed from the two curves drawn in Fig. 2. The squares represent four additional experiments, in which the labelling of a preparation in the same conditions was arrested when a given value of the response inhibition was reached. The arrest was by removal to, and repeated washing in, *d*-tubocurarine (5 $\times 10^{-3}$ M) solutions in Tyrode. The second half of the same diaphragm in each case was labelled simultaneously to saturation, and both tissues were autoradiographed, so that the percentage occupancy of the toxin-binding sites could be directly determined.

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By precisely similar methods, we have followed (ref. 21 and E. A. B. and J. W., in preparation) the effect on the muscle response of the progressive occupation by DFP of the ChE active centres. The requirement for the ChE (or the AChE) molecules for transmission is less stringent. Twitch potentiation commences when 65% of the ChE sites are inhibited, but the single twitch response persists when all of the ChE sites are blocked with DFP. Tetani evoked at 60 impulses s⁻¹ were sustained when not more than 5% of the AChE sites were free. For higher frequencies of transmission, on the other hand, appreciable amounts of the enzyme are required to remove excess acetylcholine; for example, the tetanic response at 120 s⁻¹ required about 20% of the ChE sites to be unblocked.

From our results we draw the following conclusions. (1) At several types of endplates, the number of cholinergic receptor sites is equal to the number of ChE active centres. This is not due to an identity of the two types of active centre. (2) If the receptor molecules, as well as the ChE molecules, are on the post-synaptic membrane, they are at a density of about 12,000 μ m⁻² of membrane, which is the density found^{3,4} for the ³H-DFP-reactive sites in two mouse muscle types. It is interesting that, using different methods, the same value (roughly 10,000 μ m⁻² of post-synaptic membrane) was deduced recently¹⁵ for the α -bungarotoxin binding sites in a preparation from *Torpedo* electroplaques. (3) Not more than 6 $\times 10^6$ molecules of acetylcholine are released per impulse at 37°C at the rat diaphragm endplate^{22,23}; taking the known number of DFP-reactive sites at this endplate² and the equality noted above, there are, therefore, about five cholinergic receptor sites per transmitter molecule available for single impulse transmission. Even so, there is no substantial reserve of functionally spare receptors. (4) The ChE and receptor numbers to-

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LETTERS TO NATURE

PHYSICAL SCIENCES

80 MHz Observations of the Scorpius X-1 Source

Andrew and Purton¹ discovered a weak high frequency radio source, which they identified with the strong X-ray source Sco X-1. The identification was confirmed by Ables², who also discovered significant changes in the source's flux density. A subsequent high resolution study of the region by Hjellming and Wade³ at 2,695 and 8,085 MHz showed clearly the presence of three closely spaced sources; the central source was found to be highly variable over a period of hours and was identified with the optical object associated with the X-ray source. It was noted that its flare emission tended to be considerably stronger at 2,695 MHz than at 8,085 MHz, with spectral indices of up to 1.5.

Unsuccessful efforts have been made to detect the Sco X-1 source at lower frequencies by Apparao⁴ (327 MHz) and Jauncey⁵ (408 MHz). In Jauncey's observation the region could be observed for a total time of only about 1 min. This was adequate for setting an upper limit to the intensity of the outer non-variable sources, but the chances of observing flare activity on the variable source were slight. Apparao's observations covered a total of 10 h distributed over five nights, but his sensitivity was sufficient to detect only a strong flare of ~ 0.05 flux units at 2,695 MHz with a spectral index of 1.5 continued to 327 MHz.

During four nights in May and July 1971 the 80 MHz radio-heliograph operated by the Division of Radiophysics, CSIRO, at Culgoora, NSW, was used to observe the Sco X-1 region for a total of 14 h. The observations were made by straddling the declination of the X-ray source with eight $3'.7 \times 3'.7$ beams spaced $2'.1$ apart in declination. The region was permitted to drift through the beams, which were repeatedly placed ahead of the source in a 64 s cycle; the scans surveyed an area of $15' \times 16'$ arc centred on Sco X-1. The outputs corresponding to the eight beams were recorded digitally and hour-long blocks of scans were later averaged.

We failed to detect a source in the region in any of the 14 hour long averages. The r.m.s. fluctuation in each averaged scan was ~ 0.25 f.u.; with a detection criterion of $6 \times$ r.m.s. fluctuation the upper limit to the flux density of Sco X-1 averaged over any 1 h (the duration of a typical centimetric radio flare) was 1.5 f.u. Although the two non-variable sources of Sco X-1 lie within one radioheliograph beamwidth of the central source, they would not have been detected with this sensitivity. But even one of Hjellming and Wade's weaker flares of 0.02 f.u. at 2,695 MHz would have been visible if a spectral index of ≥ 1.2 had continued to 80 MHz.

These observations combined with those of Apparao represent a total low frequency observing time of 24 h distributed over nine nights. Hjellming and Wade's observations indicate that several radio flares would be expected to occur in that time. We therefore conclude that the high spectral indices noted by

them are not continued into the low frequency end of the spectrum.

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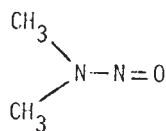
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Organic Analyses of Selected Areas of Surveyor III recovered on the Apollo 12 Mission

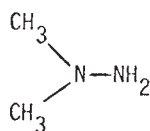
THE Apollo 12 astronauts recovered the television camera, the trenching scoop and a few smaller items from Surveyor III, which had been on the Moon for 31 months¹. They noticed that the white surfaces of the spacecraft had become tan. The television camera remained in the Lunar Receiving Laboratory (LRL) during quarantine period and afterwards preliminary microscopic visual examinations and extensive photography were conducted at the LRL. The camera was then shipped to Hughes Aircraft Company for detailed studies and disassembly. Whenever possible the camera was handled and examined in laminar flow clean areas. On close examination, optical interference patterns were found on the camera mirror. The effects of lunar particles on this mirror had been observed earlier². We report here the organic contamination of the mirror surface and camera exterior (shroud) attributable to the spacecraft outgassing, Lunar Module (LM) descent engine blasting, possible Surveyor III engine exhaust products—although thought to be unlikely due to the spatial configuration of the spacecraft components—and unknown sources. A more detailed report of these data will be published by NASA³.

The camera mirror and middle shroud were extracted for organic material by washing the surface with benzene or benzene and methanol (3:1) squirted on by a syringe and collected in a beaker. The area of the mirror which was washed with benzene was approximately 35 cm². The whole operation was carried out in a class 100 organic clean room. These wash solvents (redistilled nanograde purity), as well as the sample washes, were concentrated on a rotary evaporator and the total residues subjected to high resolution mass spectrometry. The mass spectrometer system consisted of a modified GEC-AEI MS-902 high resolution mass spectrometer on-line to an XDS Sigma 7 computer⁴⁻⁶.

The solvent background (less than 0.1 p.p.b.) consisted of hydrocarbons, chiefly the series C_nH_{2n-6} for $n=6$ to 16, and indications of carboxylic acid fragments, $C_nH_{2n-1}O_2$ for $n=3$ to 7, and phthalates (small peak of composition $C_8H_5O_3$). The residue from the mirror wash amounted to approximately 80 μg (about 2 $\mu g/cm^2$). It consisted principally of dioctyl phthalate, hydrocarbons of the series C_nH_{2n+2} for $n=3$ to 15, C_nH_{2n} for $n=3$ to 14, C_nH_{2n-2} to C_nH_{2n-10} for $n=5$ to 12 approximately, carboxylic acids of the series $C_nH_{2n}O_2$ for $n=1$ to 16 and 18 (palmitic and stearic acids were the major homologues of the series) and in minor amounts silicones and LM engine exhaust products. The silicone oil was substantiated by ions of compositions C_3H_9Si , $C_5H_{15}OSi_2$ and $C_7H_{21}O_2Si_3$, derived from straight chain silicones and ions of compositions $C_4H_{13}O_3Si_3$ and $C_5H_{15}O_3Si_3$, derived from cyclic silicones. The peaks attributable to LM exhaust^{7,8} are NH_3 , HCN , fragments CH_3NH and CH_3NCH_3 , NO , and $C_2H_6N_2O$ (I).



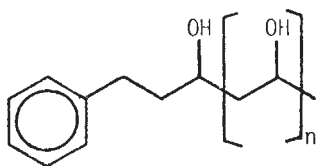
I



II

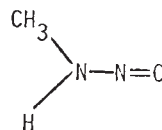
The nitric oxide is the major reduction product from the LM oxidizer, N_2O_4 . The dimethyl oxazine (I) is a partial oxidation product of unsymmetrical dimethylhydrazine (II), the LM fuel.

The middle shroud was washed with benzene and methanol on the side toward the LM and on the side away from the LM, and the extract residues amounted to approximately 120 μg (about 5 $\mu g/cm^2$) for the sample toward the LM and approximately 200 μg (about 8.5 $\mu g/cm^2$) for the sample leeward the LM. The major constituents found for both of these samples are hydrocarbons of the series C_nH_{2n+2} for $n=2$ to 29, C_nH_{2n} for $n=2$ to 19, C_nH_{2n-2} for $n=2$ to 16, with minor amounts of C_nH_{2n-4} to C_nH_{2n-10} for approximately $n=6$ to 13, dioctyl phthalate and silicone oil. This was substantiated by the same peaks in the high resolution mass spectral data as for the mirror sample. The minor components of these samples are nitrogenous and oxygenated compounds. A group of oxygenated peaks indicate a partially depolymerized vinyl alcohol-styrene copolymer (III)⁸. The peaks of compositions $C_{13}H_{19}O_3$, $C_{11}H_{15}O_2$, $C_9H_{11}O$, and C_7H_7 (tropylium ion) fit the pyrolytic fragmentation pattern for the copolymer III. The LM descent engine products are more varied in these samples than in those from the mirror wash, but still minor. Ions fitting the compositions NH_3 , HCN , probably acetonitrile and propionitrile^{7,8}, NO , CH_2NO , CH_3NO , C_2H_5NO (N-hydroxyaziridine⁸) and the fragment series $C_nH_{2n}NO$ for $n=3$ to 5 and $C_nH_{2n-2}NO$ for $n=5$ and 6 are found. The peaks of composition $C_2H_6N_2O$ (I), CH_4N_2O (IV), and CH_5N_2O (a protonated species of IV) are present in significant amounts. The methyl oxazine (IV) may possibly be derived from the Surveyor III engine exhaust, because the fuel used was mainly monomethylhydrazine (V).

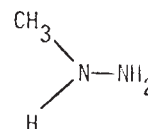


III

In summary, essentially the whole outside surface of the Surveyor III television camera was covered by lunar fines, probably from the following sources: Surveyor landing, lunar transport due to meteoroidal impacts, LM landing, and



IV



V

redistribution during return and subsequent handling. Thus the evidence for LM and possibly Surveyor III descent engine exhaust products on the shroud and mirror is not surprising. The side toward the LM was heavily sandblasted and more discoloured than the side opposite. This fact was not too well demonstrated by the organic material isolated from the shroud, except that the total ion current for the leeward sample was about double that of the sample from the side facing the LM. The same types of organic molecules were found on the mirror and both shroud samples. The sources of the various organic contaminants⁹ are as follows: hydrocarbons from lubricating oils; general terrestrial contamination from exposure and bagging material; dioctyl phthalate from polyethylene bagging material (the plasticizer); carboxylic acids from decomposition of grease and general terrestrial contamination and handling; silicones from sources as lubricating oil, outgassing of electronics and plasticizer; styrene-vinyl alcohol copolymer probably from electronics insulation; and nitrogenous compounds from LM and possibly Surveyor III engine exhaust. The organic contamination levels do not seem to contribute to the discoloration of the various surfaces.

In spite of the significant amounts of terrestrial contaminants, adsorbed mainly from exposure during examination and exhibition, as well as from the bagging materials, it was still possible to detect compounds derived from landing engine exhausts, and some compounds which may be spacecraft outgassing products. Unfortunately the LM exhaust products contaminated sample scheduled for collection by the Apollo 14 mission was not accomplished. It is rescheduled for Apollo 15. Such data will be of value in interpreting the findings of soft-landed spacecraft on other planets (for example, Viking on Mars). Furthermore, analyses for organic contaminants and identification of their sources, even if low in concentration, should be recognized as an important criterion for the design of optical or other active instruments for future spacecraft.

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Isenthalpic Flow, Joule–Kelvin Coefficients and Mantle Convection

WALDBAUM¹ has suggested that, when mantle material convects according to the model of Turcotte and Oxburgh², the temperature of an isolated rising mass will increase, “even in the idealized case where friction, viscosity and turbulence are ignored”. He argues from the premise that the steady adiabatic flow of a fluid is isenthalpic along streamlines: the Joule–Kelvin coefficient of the fluid can therefore be used to predict the temperature change during decompression.

This argument is incorrect. Waldbaum has apparently been misled by variations in the published definitions of enthalpy. Although the enthalpy of a substance is always defined by an expression of the form

$$h = u + pv \quad (1)$$

(h = specific enthalpy, u = specific internal energy, p = pressure and v = specific volume), there are important variations in the definition of the internal energy u . Of the two authorities quoted by Waldbaum, Pippard³ includes in h and u terms for kinetic and potential (gravitational) energy, whereas Liepmann and Roshko⁴ include a term for kinetic energy in what they call “total enthalpy”, but make no mention of potential energy. For them and for Landau and Lifshitz⁵, however, the unqualified term enthalpy is taken to describe an intrinsic property of a substance, dependent only on local thermodynamic variables; it is “the enthalpy which would be measured by an ‘observer’ moving with the fluid”⁴. Pippard’s definition permits him legitimately to say that, in steady adiabatic flow, the enthalpy of a fluid is constant along streamlines. For Landau and Lifshitz, however, the quantity which is constant is the sum

$$\text{enthalpy} + \text{potential energy} + \text{kinetic energy} \quad (2)$$

It can now be seen why the Joule–Kelvin coefficient ($\partial T/\partial p$)_{*h*} is not directly applicable to free convection in a gravitational field. This coefficient is defined physically for a condition of constant intrinsic enthalpy, which does not exist where decompression occurs through upward movement in a gravitational field. For a slowly moving frictionless fluid, the stress field in those circumstances must be purely hydrostatic, and in adiabatic flow the entropy (s) will be constant. Differentiating (1) and (2) gives

$$du + p dv + v dp + g dz = 0 \quad (3)$$

where g is gravitational acceleration and z is vertical height. As $vdp = -gdz$ in hydrostatic conditions, we obtain the standard equation of energy balance for reversible adiabatic expansion

$$(du + p dv)_s = 0 \quad (4)$$

The temperature gradient is therefore the well known adiabatic gradient of geophysical fluid dynamics, based on the isentropic coefficient ($\partial T/\partial p$)_{*s*}.

It might be suggested that isenthalpic heating or cooling coefficients could be applied to deviations of the stress field in a real fluid from a vertical hydrostatic gradient. Such deviations could be considered to correspond to the irreversible “isenthalpic steps” of Waldbaum’s argument. But how large are they? The topography of the mid-ocean rift suggests ~0.6 kbar near the surface, whereas Mackenzie⁶ obtained values less than 1 kbar at depths of 50 to 100 km under trenches from an analysis of gravity anomalies. Waldbaum’s isenthalpic coefficients therefore suggest temperature rises of ~20 K or less. It is also questionable whether the flow is truly adiabatic in the regions of maximum non-hydrostatic stress; as Tozer⁷ points out, when viscosity of a fluid varies rapidly with temperature, shear flow and associated viscous dissipation will tend to be strongly localized. The evidence of high heat flow behind island arcs tends to support this view⁸. Thus it seems likely that Joule–Kelvin coefficients will be of limited value in estimating temperature changes related to slow planetary convection.

Because of these problems it seemed worthwhile to examine further the variations in usage of the concept of internal energy

among thermodynamicists. Many workers bypass the problem by not mentioning gravitational and kinetic energy at all. Gibbs⁹ clearly separated gravitational energy from what he called the “intrinsic potential” of a chemical component of a thermodynamic system: he included kinetic energy¹⁰, only to show that it must vanish at thermodynamic equilibrium. Guggenheim¹¹ treats gravitational energy in the same way as Gibbs, but Lewis and Randall¹² take the alternative approach and include it in the internal energy. It is unfortunate that few authors except Lewis and Randall¹² and Denbigh¹³ point out the existing divergences, for there is evidently little prospect of reaching a consensus on this matter in the context of chemical thermodynamics. Considering the thermodynamics of fluid flow (a subject not usually discussed by chemical thermodynamicists) there is much to be said, however, for general adoption of the Landau–Lifshitz approach, because the kinetic and gravitational components of the total energy may often be analysed more or less independently of local thermodynamic parameters. In the absence of uniformity, confusion may be minimized by use of the adjectives “intrinsic” or “total” to indicate the sense in which the terms energy, enthalpy or chemical potential are being used in a particular context.

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Spontaneous Fission Previously Observed in a Mercury Source

PREVIOUSLY¹, we have presented evidence for the possible existence of a superheavy element with atomic number 112. The principal evidence for the possible existence of this element was based on the observation of spontaneous fission in a mercury source separated from a tungsten target which had been irradiated by 24 GeV protons. Spontaneous fission activity was observed, using polycarbonate foils, in mercury sources separated from two tungsten targets. These latter are identified by the symbols W2 and W3. In the case of the W3 source the proton dose was probably less than for W2 and also only about 30% of the mercury added as carrier was recovered in the final source (as measured by colorimetric techniques). The observed fission activity was smaller than that observed with the W2 source. In the latter case (W2) the measured activity was originally about three fissions/day and all experimental work reported here has been carried out with this sample.

The argument that the observed activity might be due to a superheavy element was based entirely on the prediction that element 112 will be the chemical homologue of mercury.

Such an identification may, of course, be in error because of the possibility of contamination of the sources. This topic was considered in some detail in our earlier work. In particular it was shown that the most likely spontaneously fissioning contaminant, ^{252}Cf (2.5 yr), could probably be excluded as there was no evidence for an associated alpha group (branching ratio 97%) at 6.1 MeV. Such a group would be expected to be sixteen times more intense than the observed rate of fission. In the case of the W3 target, immediately after the original chemical separation the Hg fraction gave 2.5 ± 0.6 fissions per week and the combined actinide-rare earth fraction gave 7 ± 2.5 fissions per week. Subsequent counting of X-rays in the Hg source indicated that less than 0.1% of all rare earths and actinides were present in the Hg fraction.

Since the earlier experiments, attempts have been made to identify the source of the observed fission activity more directly by trying to measure nuclear properties which depend in some way on the Z or A of the fissioning nucleus. As will be shown, this attempt has only been partially successful and the present letter is in the nature of a progress report on some continuing experiments, the results of which are of general interest.

With the aim of being able to measure the energy spectrum of the fission fragments some attempts were made to reduce the thickness of the W2 source and to make it more uniform. For these reasons the source was ozonized and mechanically spread on the Pt backing plate. While the source was still too thick to permit accurate measurement of the fission fragment energy spectrum, it was possible both to detect the fission fragments and measure the alpha particle energy spectrum simultaneously in the same silicon surface barrier detector. With this system we measured an upper limit of 5:1 for the ratio a/f , of all alpha particles having energies near 6.1 MeV to spontaneous fission activity. This indicated that at that time at most 30% of the spontaneous fission activity could have been due to ^{252}Cf . The number of fissions in the source was frequently measured with polycarbonate films over a period of 3 months after ozonization and gave an average value of 4 ± 0.3 fissions per day over this whole period. Statistical uncertainties made it impossible to determine whether the fission activity was growing or decaying.

After this period a more uniform source was prepared by chemically exchanging the Hg activity onto an evaporated film of PbS on a $240 \pm 20 \mu\text{g cm}^{-2}$ polycarbonate backing. Roughly 50% of the fission activity was transferred onto the PbS film. With this source it was now possible to measure the

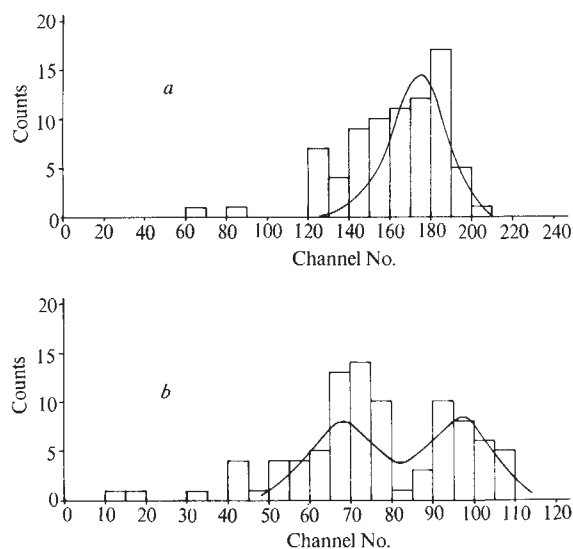


Fig. 1 Energy spectra of fission fragments observed with the mercury source. In *a* the summed kinetic energy spectrum is given, and in *b* the singles spectrum observed with the front detector. The continuous lines show similar measurements with a ^{252}Cf source with much better statistics.

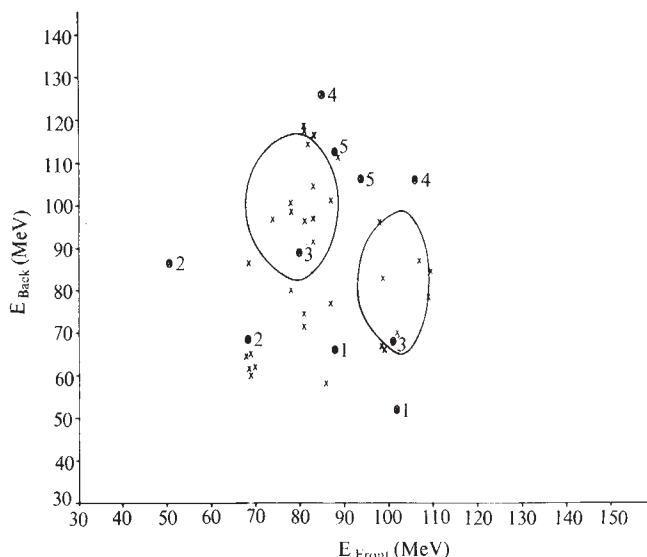


Fig. 2 Correlated energies of fission fragments from the Hg source. The pairs of numbered points show the alternative interpretations when the analysis of the events is ambiguous. The contours enclose the region in which 90% of ^{252}Cf fragments would be found and are asymmetric because of energy loss in the source backing.

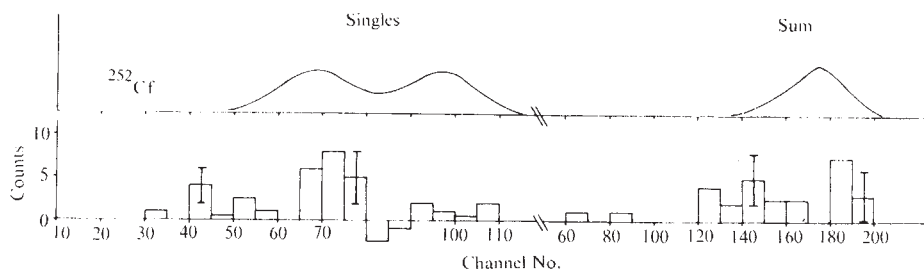
kinetic energy spectrum of the fission fragments and energy spectra were measured with two silicon surface barrier detectors for both single and coincident summed kinetic energies. The observed spectra are shown in Fig. 1. We also show in Fig. 1 the spectra obtained in the same apparatus from a ^{252}Cf source which was prepared by sublimation of ^{252}Cf onto successive layers of PbS to simulate the HgS-PbS source as closely as possible. Clearly source thickness and non-uniformity could greatly affect the spectral shapes.

Fig. 1*a* shows that the two sum spectra appear to differ in shape particularly in the low energy region and that the Hg sum energy spectrum seems to have a peak at slightly higher energy than that for ^{252}Cf (roughly 194 MeV, as compared with 182 MeV for ^{252}Cf). Because of the difference in spectral shapes, however, the average value of the sum kinetic energy for the Hg source is lower than that of ^{252}Cf . The possibility of non-binary fission cannot be ruled out for superheavy elements, so any conclusions based on the assumption of binary fission must be regarded with caution. In addition, if multiple fission occurs, our two detector system will not in general measure the total energy. With this in mind, it is worthwhile noting that since the total kinetic energies for binary fission are roughly proportional to $Z^2/A^{1/4}$, then fragments from the binary fission of element 112 would be expected to have a total kinetic energy 24% higher than that for ^{252}Cf (or about 225 MeV) whereas those from Hg isotopes would be expected to have a total kinetic energy of about 130 MeV. A statistical χ^2 analysis indicates that the probability that the observed sum spectrum is consistent with that of pure ^{252}Cf is less than 1%. This probability increases to 30% if the point with the largest value of χ^2 (at channels 120-130) is removed from consideration.

The energy spectrum of single fission fragments from the W2 source is shown in Fig. 1*b*. The two peaks in the spectra are in similar positions to those measured for a ^{252}Cf source under the same conditions. The ratio of the heights of the high energy to low energy peaks is $0.7 \pm 0.2:1$ for the Hg source compared with a value of 1:1 measured for the ^{252}Cf source.

The fission data were printed out sufficiently often that about 50% of the individual singles and coincidence events could be correlated with each other. In these cases, it is possible to determine the energy of the fission fragments striking the back detector by a simple subtraction. The energies of the correlated fragments are plotted in Fig. 2, together with a contour

Fig. 3 Fission energy spectra for coincident and singles events after subtraction of a ^{252}Cf kinetic energy spectrum normalized to 70% of the total number of fission counts. Also shown for comparison are spectra obtained with a ^{252}Cf source.



which encloses the region in which 90% of the ^{252}Cf fragments would be found. The relatively large number (30%) of the observed fissions from the Hg W2 source which do not fall within the contours can be regarded as evidence of spontaneously fissioning material other than ^{252}Cf in the Hg W2 source.

Using the same thin mercury source another measurement was made of the ratio of intensity of 6.1 MeV alpha particles to fission fragments. The value obtained was $\alpha/f = 11 \pm 1.5$ to be compared with the known value $\alpha/f = 16$ for ^{252}Cf . If the 6.1 MeV alpha particles are associated entirely with the disintegration of ^{252}Cf this would imply that $\sim 70\%$ of the observed fission activity at that time stemmed from ^{252}Cf .

Using the same W2 mercury source a measurement of the mean number of neutrons emitted per fission ($\bar{\nu}$) was made using the apparatus described by Mather *et al.*². In the present measurements the requirement for a coincidence between the fission fragment and a prompt gamma ray was omitted. The value of $\bar{\nu}$ obtained in this way was 3.7 ± 0.5 which when compared with the known value of $\bar{\nu} = 3.76$ for ^{252}Cf again suggests that a significant fraction of the activity could have been due to this element.

Measurements of the fission energy spectra, the mean number of neutrons per fission and the alpha/fission intensity ratio all suggested that a significant fraction of the observed fission activity from the thin source could have been due to ^{252}Cf . Further chemical separations were therefore carried out on the Hg source from the W2 target to give both mercury and actinide fractions. Measurements of the fission and alpha activity of the resulting actinide source showed that $73 \pm 7\%$ of the fission activity observed at the time of the kinetic energy measurements now appeared in the actinide fraction and here the 6.1 MeV alpha to fission ratio was $16 \pm 2 : 1$ indicating that this fission activity was probably due to ^{252}Cf .

With the Hg fraction an attempt was made to exchange the Hg onto a PbS coated film. Approximately 70% of the original Hg tracer and no detectable ($< 1\%$) rare earth tracer were found in this HgS-PbS source. Using a surface barrier detector in the same geometry as for the original source about 3% of the fission activity (1 ± 0.5 per week) was found in the HgS-PbS source. The ratio, α/f , for this source for the few alpha particles observed between 6.05 and 6.15 MeV was found to be $4.7 \pm 4 : 1$. A subsequent 2 week measurement of the fission activity of this source with a polycarbonate film gave no events. The source from the residual solution was too thick to be counted.

From these measurements it appears that approximately 70% of the fission activity now observed from the W2 source is due to ^{252}Cf although the remaining 30% seems unlikely to be due to this element. As early alpha spectra showed smaller amounts of alpha activity having an energy of around 6.1 MeV for comparable rates of fission activity we conclude that after the original separation either the source has been contaminated or the ^{252}Cf has grown in. The frequent changes in source geometry and low counting rate make it difficult to distinguish between these possibilities. It is not possible to explain the changes in alpha to fission ratio as being the result of changes in source thickness as the alpha particles have a range which is larger than that of the fission fragments.

Finally, in Fig. 3 we show the results of the fission energy spectra measurements after subtraction of a ^{252}Cf kinetic energy spectrum normalized to 70% of the total number of

fission counts. Within the very large statistical uncertainties of these residual spectra it appears that the total kinetic energy spectrum either shows two peaks (one broad peak centred about 150 MeV and one at about 195 MeV) or one very broad peak (centred at about 170 MeV). The single spectrum shows three regions: two broad regions centred at about 65 and 100 MeV and a sharper and more pronounced peak at 85 MeV.

The Hg W2 source used for the kinetic energy measurements was placed on an Ilford K-1 nuclear emulsion for 13 days before the final chemical separation. Examination of the tracks in this emulsion gave an upper limit of 0.5 non-binary fissions per day (about 30% of the "non-Cf" fissions).

The fact that the measurement of $\bar{\nu}$ for the total Hg source was close to that of ^{252}Cf indicates that the remaining 30% of the fission activity has a neutron multiplicity in the range of 2 to 5. The distribution of multiplicities did not indicate any events of multiplicity 7 or greater and also no large preponderance of events of multiplicity 1.

To summarize, both the alpha to fission ratios and subsequent chemical separations show that at the time of our kinetic energy measurements 70% of the fission activity was due to ^{252}Cf . After subtraction of the ^{252}Cf component the residual fission kinetic energy spectra differ considerably from those of known actinides. An unlikely explanation is that the distribution of kinetic energies could indicate a mixture of spontaneously fissioning species, one in the light Hg-Po-Ra region (but see ref. 3) and one in the heavier No-Lw region. Another possibility is that it could be the spectrum of fragment energies produced in an unusual mode of fission such as predicted by Greiner⁴ for superheavy elements. It must be noted that the kinetic energy spectra and the value of neutron multiplicity do not agree with the published predictions for binary fission of superheavy elements; however, neither do the kinetic energy spectra appear to fit those of any known spontaneously fissioning actinide isotope.

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maximum cross section of 20 mbarn at a bombarding energy of 370 MeV. The total cross section for $^{74}\text{Ge}(\text{Kr}, \text{xn})$ reactions of 32 mbarn was found to be in agreement with theoretical estimates based on the concept of critical angular momentum^{4,5}. This shows that the total fusion can be represented by:

$$\sigma_{\text{CF}} = \pi \hbar^2 \frac{l_c^2 c}{2\mu \bar{e}}$$

where l_c is the critical value of the angular momentum quantum number, μ is the reduced mass and $\bar{e}$ the centre of mass energy. Studies of the reactions $^{116}\text{Cd} + ^{84}\text{Kr} \rightarrow ^{197}\text{Po} + 3n$ at a bombarding energy of 375 MeV and $^{164}\text{Dy} + ^{40}\text{Ar} \rightarrow ^{200}\text{Po} + 4n$ at 190 MeV gave cross sections of 3 mbarn and 25 mbarn, respectively, demonstrating the effect of the enhancement of the fission width because of the larger angular momentum of the krypton projectiles, and the decrease of fission barriers for light polonium isotopes.

After the successful demonstration of the technique and with the confidence placed in the theoretical prediction of the cross sections by the above results we bombarded a thorium target with 450 MeV Kr^{23+} ions for 10 h. No activity was observed—probably because the energy was near the Coulomb barrier—and the experiment was repeated with 500 MeV Kr^{24+} ions on a 1 mg cm^{-2} thorium target. The alpha spectrum obtained at this energy is shown in Fig. 1. Energy calibrations with the thoron deposit (8.78 and 6.05 MeV) and with ^{153}Er (4.67 MeV) and ^{152}Er (4.80 MeV) are shown with larger arrows. Many alpha particles of energy between 7 and 9 MeV have been assigned to light isotopes of polonium, astatine or radon which might have been produced by fission of very heavy nuclei. The absence of ^{212}Po at 8.78 MeV is significant. The peaks at 8.1 MeV, 8.48 MeV might be attri

Complete Fusion induced by Krypton Ions: Indications for Synthesis of Superheavy Nuclei

COMPLETE nuclear fusion has been produced by bombarding targets of germanium, cadmium and thorium with 450 MeV Kr^{23+} and 500 MeV Kr^{24+} obtained from the Orsay accelerator ALICE¹. Recoiling synthesized nuclei were slowed down in helium gas, transferred through a capillary tube and deposited on a steel rod in an evacuated enclosure². An annular silicon semiconductor counter around the capillary tube detected the alpha particles produced by the decaying nuclei. Typical bombardment times were of the order of 10 h with 10^8 Kr ions s^{-1} , and the background was shown to be insignificant by bombarding for 24 h without a target in place. Further tests also showed that secondary neutrons and gamma rays did not induce nuclear reactions in the detector.

The apparatus was tested by carrying out experiments with an argon beam and a dysprosium target³ that produced the known alpha emitters ^{200}Po and ^{199}Po . Also the reaction $^{84}\text{Kr} + ^{74}\text{Ge} \rightarrow ^{153}\text{Er} + 5n$ was studied and found to give a

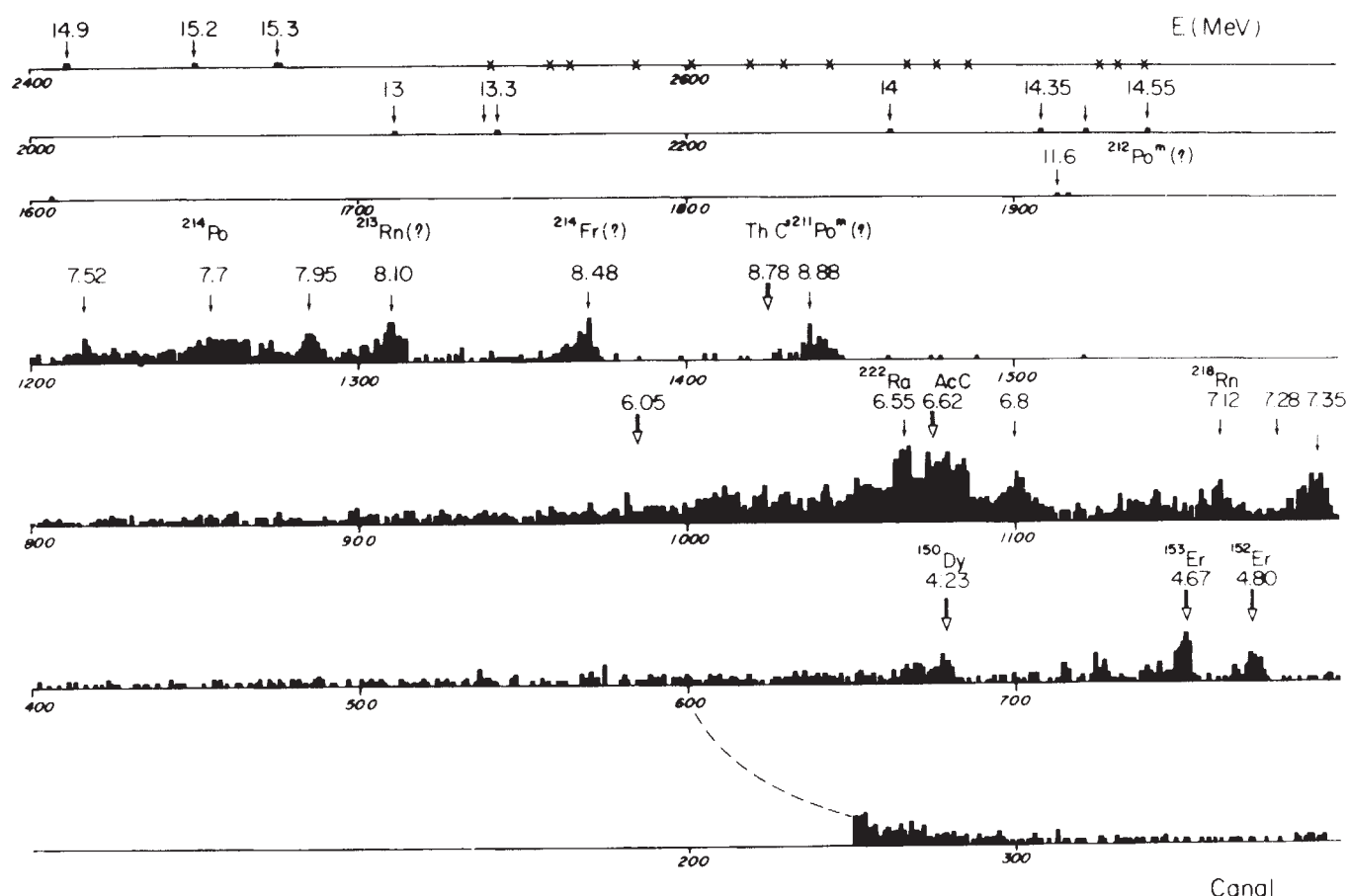


Fig. 1 Pulse height spectrum of particles obtained with a semiconductor annular junction detector. Energy calibration is indicated by large arrows. Crosses represent counts which have been dismissed by the study of the stopping power. (Target ^{232}Th , projectiles Kr^{24+} at 500 MeV.)

buted to isotopes 254 and 256 of element 102. At 8.9 MeV, the alpha rays cannot be attributed to $^{211}\text{Po}^m$ since the corresponding 91% branch at 7.28 MeV was not observed. The most significant result is the observation of pulses corresponding to alpha energies higher than 9 MeV, which had not been found at 450 MeV bombardment.

To ensure that the particles responsible for such pulses were indeed alpha particles, a thin aluminium foil was put in front of the detector and the experiment repeated twice for a full bombarding time of 10 h each. By this method several pulses corresponding to energies larger than 16 MeV were dismissed. They were probably the result of coincidences of alpha particles from a nucleus and its daughter when the disintegration half life of the daughter is shorter than the pulse length of 1 μs . The other events have been shown to be due to alpha particles of energies between 13 and 15 MeV. The cross section is of the order of 10 μbarn for the nuclei which emit these particles and their half life lies between 10^{-3} s and 1 min. Because of the conditions under which the alpha particles are produced they might come from superheavy isotopes for which the theory⁶ predicts alpha disintegrations of 13 to 14 MeV with half lives of ms. It is not possible to attribute 13 or 14 MeV alpha particles to elements of atomic numbers less than 102 with a half life as long as 1 ms. These results can be taken as an additional indication for the existence of super-heavy elements first observed by Marinov *et al.*⁷ in a very different experiment.

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Late Precambrian Glaciation: an Anti-Greenhouse Effect?

A GLACIATION in the latest part of Precambrian time¹ is commonly accepted as a major, rapidly waxing and waning event. Most of the northern hemisphere was involved².

Before that glaciation major limestone or dolomite bodies are often developed; for example in Finnmark, northern Norway, the original type area for the "Varanger" Glaciation. Here, a Porsanger Dolomite Formation reaches 250 m thick over 60 km outcrop and appears only part of a much larger carbonate body stripped off in the glaciation.

Spencer gives full details of similar events in the Scottish Dalradian³. These thick carbonate horizons may be linked with sealevel fall; that is, the withdrawal of seawater into ice-caps.

I am now inclined to think that the very thickness of these carbonate bodies^{4,5} argues against that idea. And, in my own area, there is preliminary stromatolite evidence taking the age of the lowest part of the Porsanger Formation as far back as 900 m.y.

If the carbonate deposition did not depend on the glaciation, did the glaciation depend on the carbonate deposition? Discussing the development of the atmospheres of Earth, Mars and Venus, Rasool and de Bergh⁷ suggest that increase of carbon dioxide in the Earth's atmosphere led to gradual heating.

Rubey estimates that some 6.7×10^{22} g of CO_2 is now locked up in sedimentary rocks. Most of this is presumably Carboniferous, Mesozoic and Tertiary—not late Precambrian. Yet, if there is an important CO_2 threshold effect⁷, then perhaps even this less voluminous trapping of the gas in late Precambrian times had serious effects on the temperature, producing a fall of temperature which was a major factor in the onset of the glaciation.

If this glaciation were in some real sense the result of locking up of carbon dioxide, why did this start to happen in the first place? There are three somewhat interdependent alternatives:

(1) Cloud⁹ suggests that these were times when an ozone screen first became effective, shielding organisms so that they could colonize open areas. Before, life was restricted in reproduction to sheltered spots, severely limiting photosynthetic activity. A change such as Cloud suggests would produce (a) general spread and massive increase, perhaps over 1–200 m.y. of earlier, presumably largely chemautotrophic life (b) with increase in population, an enormously enlarged gene pool, with attendant increase in rate of evolution.

Where restricted marine basins developed, there could be great increase in carbonate deposition biologically controlled.

(2) Alternatively, the carbonate bodies developed at this time because this was a phase of extreme peneplanation, such as in much of the Jurassic and Cretaceous. No glaciation followed then.

(3) Valentine and Moores¹⁰ discuss the regulation of sealevel in terms of plate-tectonics. If the rapid plate movements of the past 100 m.y. occurred in Vendian times then the effect on sealevel of those movements may have been very great.

This could be seen as providing the right place for shallow water sediments during the major burst of evolution suggested in (1).

Crowell and Frakes¹¹, discussing the later Gondwana glaciation, propose that glaciation here was not short-lived but extended through most of Palaeozoic time. Areas were glaciated as they moved across the polar region. According to them, glaciation had more to do with changes in the atmosphere/ocean circulation than anything else. Their proposals cannot be examined here, but it may be that we have accepted a sudden glaciation in late Precambrian times because of its vital role in the stratigraphy of otherwise very confused areas.

The idea of an anti-greenhouse effect should be examined in two ways: (a) In the light of local geology—what was the local sedimentary background to the carbonate deposit and the tillites? (b) How does it relate to other theories of glaciation, and to the problems of the Proterozoic/Phanerozoic boundary?

The anti-greenhouse effect could be a new argument for rapid onset of the Late Precambrian Vendian glaciation. Crowell and Frakes or, more recently, Crawford and Daily's¹² objections to rapid waxing and waning of the Vendian glaciation seem to be based on comparison with the apparently very different conditions of the Gondwanaland Palaeozoic Glaciation.

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Are the Astrophysical and Statistical Schools of Irreversibility Compatible?

A SERIOUS crisis at the foundations of natural sciences has been generated recently by the astrophysical school of thought¹⁻⁴ which maintains that the origin of irreversibility and all time asymmetries observed in nature can be traced back to initial conditions which gave rise to the present expansion of the universe as a whole. The astrophysical school has been considered to be in serious contradiction to the more established statistical school⁵ which claims that irreversibility and time asymmetries originate in the nature of macroscopic observations; that is, in the macroscopic instrument which records information and which retains a record of it. I wish to show how both schools of thought are essentially compatible with each other in particular from a cosmological viewpoint of entropy-free thermodynamics⁴.

First, I stress, in agreement with Beauregard⁶ and Bergmann⁷, that the introduction of statistics into the time sym-

metric laws of (classical or quantal) mechanics does not by itself produce irreversibility. Thus to obtain the statistical time asymmetry one must add a specific postulate of asymmetry, for example, the initial (not final) condition stating that "blind statistical retrodiction is forbidden". Second, I refer to a few broad aspects of the Hogarth-Gold-Narlikar-Gal-Or school of thought¹⁻⁴ which explains how the first cosmological asymmetry (Fig. 1) is linked, in a one to one fashion, to all other time asymmetries that are in evidence. In supporting this school of thought Beauregard⁸ maintains that if a reflecting box is not expanding, all enclosed quantal systems will keep fluctuating around an equilibrium energy state, exchanging quanta on stationary waves. But if the reflecting box is expanding, all enclosed quantal systems will be decaying and emitting quanta on all sorts of electromagnetic, electronic, neutronic and so on, waves. More specifically Beauregard feels that space expansion goes hand in hand with a general decay of gravitating sub-systems, and general emission of gravitons on the corresponding retarded waves. The last were shown by Narlikar³ to be generated by the world's expansion (which, in turn, can be traced back to initial conditions imposed on time-symmetrical field equations) out of the time-symmetrical Wheeler-Feynmann theory. As to the microscopic time asymmetry in elementary particles Aharony and Ne'eman⁹ have recently demonstrated (for the evolution of the $K^0-\bar{K}^0$ complex) a one to one relation with the cosmological asymmetry.

According to the statistical school¹⁰, however, any finite region of the universe should have a finite relaxation time and should be in equilibrium—a condition unfulfilled throughout the universe accessible to our observations (note the redshift, Hubble's law, and the irreversible photon expansion into the inter-galactic non-reflecting space). The escape from this contradiction as well as from the Olbers' "paradox" can first be traced to the redshift which operates to diminish the radiation fields. Thus the sky is dark (and thus plays the role of a huge "thermodynamic sink") because in most directions the material on a line of sight is receding. Inside non-expanding galactic bodies, as we know from observations, the transfer

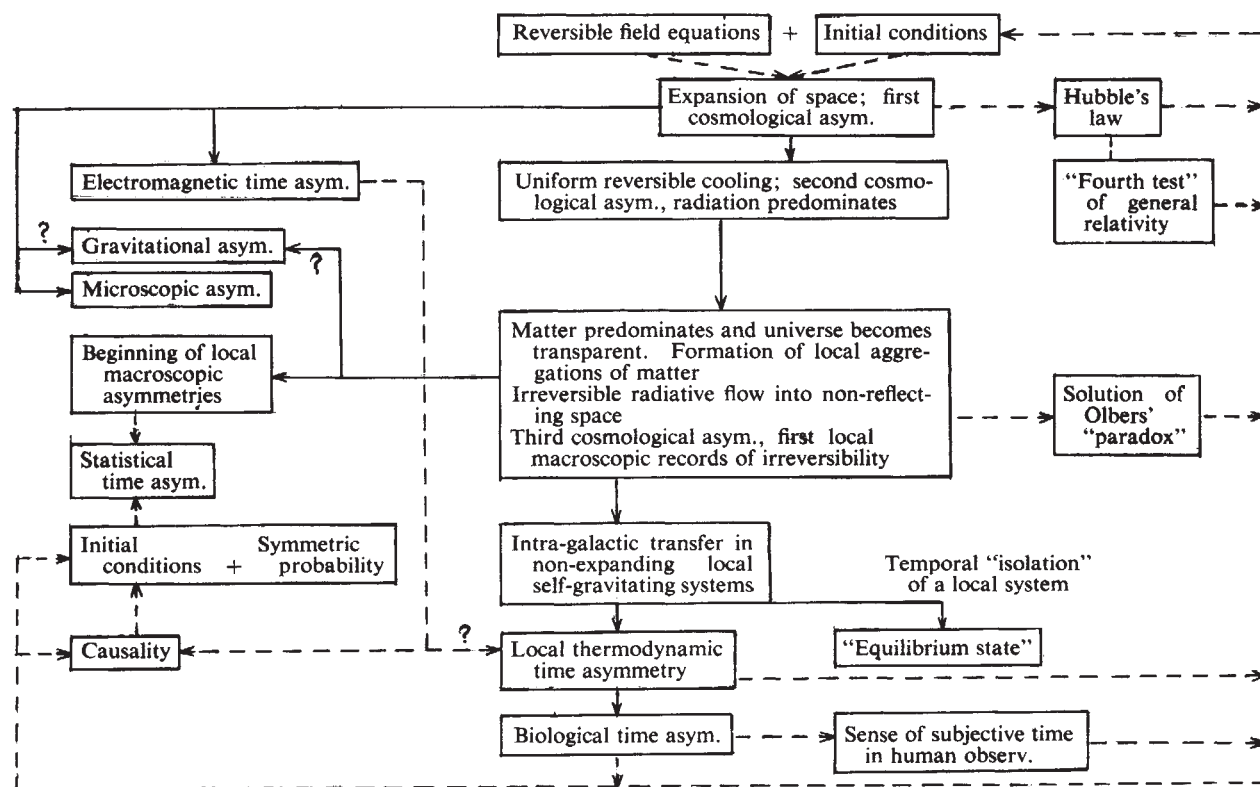


Fig. 1 The main sequence of links according to the astrophysical school¹⁻⁴ of the origin of irreversibility in nature. Solid lines represent expected physical links.

of energy involves a very large number of intermediate stages which include such local processes as conduction, convection, chemical and nuclear reactions. But because the net result is a continuous emission of energy from galactic surfaces any energy released inside them should, eventually, find its way out into the expanding space (which never reaches "equilibrium state"). The time constant for intra-galactic transfer depends therefore on the scale, position and details of the system inside non-expanding galactic aggregations. The time constant of a local system may be estimated in the laboratory by a temporal "isolation" (through imposition of "time-invariant" boundary conditions interacting with external non-equilibrium systems which supply the required energy) during which time asymmetry persists for a while but eventually vanishes. This mechanism explains the occurrence of local "equilibrium states", in an overall non-equilibrium surrounding. It also explains how the first cosmological asymmetry dictates all local processes far away along the world lines.

Yet, very convincingly, the statistical school maintains⁵ that irreversibility has its root in the very process of observation or more specifically in the macroscopic instruments which record information. In trying to reconcile the two schools of thought I first raise the question: what might be the earliest possible local macroscopic instrument to record irreversibility in an expanding (or contracting) universe? My lemma is that the origin of irreversibility defined thus can be traced back in time to the period when the first local self-gravitating aggregations of matter had started to form out of an isotropic and uniformly expanding universe. This proposition is based on the assumption that before the formation of local irregularities of matter the universe was uniform with radiation making an overwhelmingly dominant contribution to the pressure (in equilibrium with uniformly scattered nuclei). As the expansion proceeded the uniform temperature fell reversibly (the second cosmological asymmetry). At about 3,000 K electrons were captured by nuclei and remained in bound orbits. At this state they no longer scattered photons and the universe became transparent. Therefore, aside from the problem that we are still far from understanding in detail the formation of self-gravitating aggregations of matter, we arrive at the conclusion that local macroscopic information of irreversibility was not in existence at the earliest period (at least 10^5 years) when there was already at least one clear and dominating cosmological asymmetry. Consequently, to affirm one school and deny the other would result in a contradiction in a non-uniform expanding world; in considering a uniform expanding world, however, the astrophysical school supplies a more universal theory about the original asymmetry of nature and the sequence of relationships which links it to all asymmetries that are now in evidence.

As another example I consider criticism of the astrophysical by the statistical school. This claims that there is no direct evidence for the relevance of cosmological effects on the nature of the viscosity of a gas¹¹. Previously⁴, I showed how the world's expansion can serve as a point of departure in laying a new basis for the second law of thermodynamics. A new entropy-free thermodynamics was thus constructed in which the second law was derived from the first law. Considering small adiabatically expanding regions with real, viscous media the entropy-free theory reduces to

$$-P_0^c \frac{dV_0}{dt} - \frac{1}{\rho} \bar{\pi} : \text{grad } \bar{v} = \frac{dU_0}{dt} = 0 \quad (1)$$

where P_0^c is the proper hydrostatic (or radiation) pressure, V_0 is the specific volume, U_0 the specific internal energy, ρ the total density, $\bar{\pi}$ the viscous stress tensor, $\bar{v}$ the centre of mass velocity vector, and t the time. Now for all real gases the adiabatic expansion of space dictates

$$P_0^c \frac{dV_0}{dt} > 0 \quad (2)$$

Consequently I obtain

$$\left(-\frac{1}{\rho} \bar{\pi} : \text{grad } \bar{v} \right) > 0 \quad (3)$$

Assuming Newtonian gases (without specifying the sign of the viscosity) equations (1) to (3) require that

$$\mu = \rho P_0^c \frac{dV_0}{dt} (\Phi_v)^{-1} > 0 \quad (4)$$

where Φ_v is the dissipation function which by its mathematical nature is always positive. The world's expansion dictates, therefore, a positive viscosity parameter. Some similar findings can be obtained for non-Newtonian fluids.

In general, the theory I postulated⁴ allows one to construct an entirely new and entropy-free thermodynamics in a close analogy to extant, entropy-based, non-equilibrium phenomenological or statistical theories.

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BIOLOGICAL SCIENCES

Reduction of Catechol-O-methyltransferase Activity by Chronic L-Dopa Therapy

THE use of large doses of L-dopa, the immediate precursor of dopamine, in the symptomatic treatment of Parkinsonism has prompted investigation of the effects of this amino-acid on enzymes involved in catecholamine metabolism. It has been found that the activity of enzymes mediating the synthesis of catecholamines, such as tyrosine hydroxylase¹ and aromatic L-amino-acid decarboxylase (personal communication with W. Dairman and S. Udenfriend), diminishes during prolonged L-dopa administration. Conversely, monoamine oxidase, one of the enzymes involved in catecholamine degradation, has been found to increase in the tissues of animals given L-dopa² as well as in the serum of patients treated with this drug³. We now report a substantial decline in the activity of catechol-O-methyltransferase (COMT), another enzyme important in mediating catecholamine catabolism, in the red blood cells of Parkinsonian patients receiving chronic L-dopa treatment.

Red blood cell COMT activity was assayed⁴ on two to ten occasions in seventeen patients. Red blood cell indices, reticu-

locytes and complete blood counts remained normal in all patients studied. Control subjects (five men and four women with a mean age of 57 yr) had received no drugs for at least 2 weeks before the study. Only one of this group had been exposed to L-dopa, but the drug had been withdrawn 2 months beforehand. Patients in the L-dopa treatment group (three men and five women with a mean age of 58 yr) had received L-dopa for 1–20 months (mean 11.8 months). Two of these individuals were receiving optimal therapeutic doses of L-dopa alone; four were receiving L-dopa in combination with α -methyl-dopahydrazine (MK 486, Merck Sharp and Dohme), an extracerebral inhibitor of aromatic L-amino-acid decarboxylase, and the remaining two patients had two or more COMT determinations while being treated with L-dopa alone as well as in combination with α -methyl-dopahydrazine. The dose of L-dopa when given alone ranged from 2.9 to 11.2 g/day (mean 6.0 g/day) and from 0.43 to 4.0 g/day (mean 1.4 g/day) when given with the peripheral decarboxylase inhibitor. Red blood cell COMT activity in control subjects did not differ significantly from levels previously found in normal individuals or in patients with schizophrenia⁵. COMT activity was 40% lower in L-dopa-treated patients (Fig. 1). No difference could be discerned between COMT levels in patients receiving maintenance doses of L-dopa alone or in combination with α -methyl-dopahydrazine.

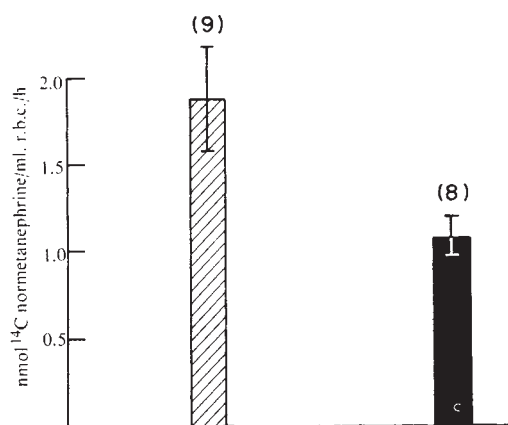


Fig. 1 COMT activity in Parkinsonian patients with L-dopa (black column) and without L-dopa (hatched column) therapy. Values shown are the means ($\pm$ s.e.m.) of each group. COMT levels were significantly lower in the L-dopa-treated group ($P < 0.05$; Student's *t* test). Blood samples were usually obtained in the early morning. Patient fasted during the preceding 10–12 h. In the treated group, samples were drawn approximately 12 h after the last dose of L-dopa.

The acute effects of L-dopa as well as the effects of duration of therapy were studied in several patients. A single intravenous dose of L-dopa (1 mg/kg) was given to three previously untreated patients. There were no measurable differences in COMT levels before injection or 0.5 and 6 h after injection. Six of the untreated patients (three men and three women) were then given therapeutic doses of L-dopa and studied for 4–16 weeks (Fig. 2). There was a significant reduction in COMT activity by the third week of treatment. By the fifth week, red blood cell COMT levels had decreased to 51% of the level before initiation of L-dopa treatment. In our patients, COMT levels seemed to vary as a function of duration of therapy but were unrelated to total daily dosage. Patients who showed an adequate clinical response to relatively low doses of L-dopa, however, seemed to have a lower COMT activity than those patients requiring relatively large doses.

To assess the specificity of these observations, the effects of L-dopa on the activity of histamine N-methyl transferase and a methanol-forming enzyme were examined. The activities of both of these methyltransferases, assayed according to Axelrod

and Cohn⁴, were not different from samples from normal volunteers run simultaneously with these patients, or from untreated patients with Parkinsonism.

To investigate the possibility that L-dopa directly influences COMT activity, *in vitro* specimens were pre-incubated for 15 min with 10^{-4} and 10^{-6} M L-dopa. Activity was not significantly altered. Dialysis for 6 h of specimens from L-dopa-treated patients with low COMT activity against 0.005 M phosphate buffer (pH 7.5) did not increase COMT activity, excluding the possibility of an easily dialysable inhibitor.

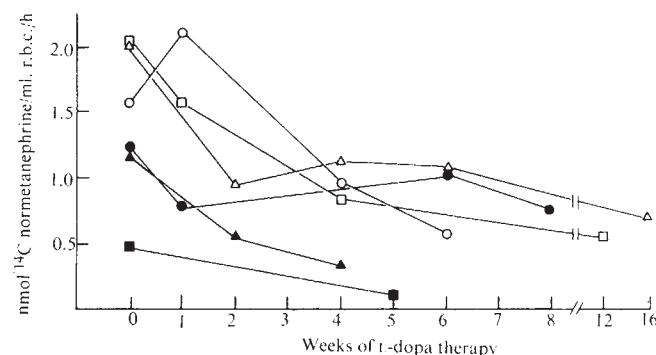


Fig. 2 Reduction in red blood cell COMT activity with L-dopa therapy. Each symbol represents one of the three men and three women studied longitudinally. Age ranged from 52–68 yr (mean = 57). L-Dopa administration was begun at time 0, after initial blood samples were drawn. Patients were studied for up to 16 weeks, during which time COMT activity declined, reaching significance after 2 weeks ($P < 0.05$; Student's *t* test).

Enzyme changes in the anucleate red blood cell may represent a unique situation, not seen in tissues capable of synthesizing new enzyme or substrate. To account for reduced COMT levels in the red blood cell, one must postulate either diminished synthesis by precursors, increased degradation or inhibition of the enzyme. Dialysis experiments have ruled out the presence of a small dissociable inhibitor; the rapidity of decline in COMT activity relative to the normal red blood cell turnover of 120 days argues against diminished enzyme synthesis in red blood cell precursors. The data are most compatible with increased enzyme lability.

Several clinical studies have suggested a tendency for L-dopa dose requirement to decrease over a period of weeks or for the clinical effects of the drug to increase gradually at a fixed dose^{6,7}. The finding of reduced red blood cell COMT activity, if representative of the effect of chronic L-dopa treatment on COMT activity in other tissues, may be relevant to this phenomenon.

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Physicochemical Stereospecificity in Taste Perception of α -D-Mannose and β -D-Mannose

THE anomers α - and β -D-mannose differ structurally only in that H and OH at the C₁ atom of the pyranose ring are interchanged. In spite of this apparently minor difference in structure, it has been suggested that the ambiguity of taste perception of D-mannose is due to actual differences in taste between the two anomers of this substance; the evidence presented in support of this view, however, was indirect because insufficient pure β -D-mannose was available for direct taste tests on that anomer¹. Sufficient pure β -D-mannose was therefore prepared for a direct and statistically reliable comparison. It was found that the subjects reliably reported the α -anomer as sweet and the β -anomer as bitter. As before, the equilibrium mixture was found to be an ambiguous stimulator.

The β -anomer was prepared by dissolving 26 g of α -D-mannose in 15 ml. of water with heating. Glacial acetic acid (15 ml.) was added to the cool syrup and the resulting solution was filtered through finely divided charcoal under reduced pressure. The funnel was rinsed with 10 ml. of glacial acetic acid and the solution was seeded with about 1 mg of β -D-mannose². A little crystal growth was noted after 24 h. Crystallization was allowed to proceed for 6.5 yr with occasional agitation, at which time sufficient (about 2 g) crystalline material was available for analysis and testing. The crystals were removed mechanically from the mother liquid, washed successively with glacial acetic acid and with absolute ethanol, and dried *in vacuo*. Infrared spectra were obtained using the KBr pellet technique. Peaks were found at 1170, 936, 899, 860, 772, 730, 620, and 448 cm⁻¹, corresponding to the characteristic peaks of β -D-mannose^{2,3}. For the α -anomer peaks were found at 971, 960, 915, 885, 831, and 812 cm⁻¹, corresponding to the known characteristic peaks of this substance^{2,3}. The equilibrium mixture used was that prepared by Steinhardt *et al.*¹, the spectrum of which confirmed that it contained both the α - and β -anomers in the equilibrium ratio.

Subjects for the taste discrimination tests were five males and five females, aged 19–24 yr. Subjects were instructed not to eat, smoke, nor to drink anything but water for 2 h before the taste tests. Each was given six to ten preliminary trials in which taste stimulators of known characteristics were presented for the purpose of subject screening and familiarization with experimental procedures. Dextrose and a dilute quinine solution were used to establish standards for sweet and bitter, respectively, and α -D-mannose containing a trace of β -D-mannose served as an ambiguous stimulus. The criteria for sensitivity and acceptability of the subject were the responses "sweet" to the dextrose and "bitter" to the quinine solution. After acceptable preliminary trials, each subject was given thirteen test trials which included four α -D-mannose samples, four β -D-mannose samples, four equilibrium mixture samples, and one dextrose sample as a control. The samples were arranged in different random orders for each subject and were administered in the solid state to avoid mutarotation. Weights were 14 mg of α -D-mannose, 6 mg of β -D-mannose, 20 mg of the equilibrium mixture, and 20 mg of dextrose. (The amounts of the α - and β -anomers correspond to the ratio in which they occur in the equilibrium mixture.) Tests were conducted using a double blind procedure. On each trial the experimenter placed the test material on the tongue of the subject who was then instructed to manipulate the substance between the tongue and the hard palate. During the test the subjects recorded their taste sensations as a function of time by depressing one of four appropriately labelled buttons on a response indicator and an operations recorder was used to record the responses "no taste," "sweet," "bitter," and "indistinguishable taste". Following each trial, after the "no taste" button had been pressed, the subject rinsed his mouth with water and was given a short rest period before the next trial.

The responses of two subjects were not included in the experimental results: One failed to follow the instructions not

Table 1 Frequency of Taste Responses to Anomers of D-Mannose and to Dextrose

	Bitter	Sweet	Sweet-bitter	Indistinguishable	Total
β -D-Mannose	30 (93.75%)	0 (0.0%)	2 (6.25%)	0 (0.0%)	32
α -D-Mannose	0 (0.0%)	30 (93.75%)	0 (0.0%)	2 (6.25%)	32
Equilibrium mixture	23 (71.88%)	2 (6.25%)	5 (15.62%)	2 (6.25%)	32
Dextrose	0 (0.0%)	8 (100.0%)	0 (0.0%)	0 (0.0%)	8

to smoke before the test and the other tasted the dextrose control as "bitter".

Subjects' responses to the substances tested are summarized in Table 1. Each of the responses was coded +1 for sweet, -1 for bitter, and 0 for indistinguishable taste. The mean coded scores for the α - and β -anomers were +0.9375 and -0.9375, respectively. For purposes of statistical analysis it was assumed that the 64 observations made were randomly and independently chosen from 16 normal populations with equal variance. The analysis showed that the specific anomer administered significantly influenced the subjects' reports of their taste sensations ($f=787.5$, d.f. 1/7, $P<0.005$). Thus, subjects very reliably reported a sweet sensation in the presence of α -D-mannose and a bitter sensation in the presence of β -D-mannose.

It seems that the so-called "ambiguity" of taste associated with D-mannose is due solely to the slight difference in the molecular structure between α -D-mannose and β -D-mannose. These results confirm the conjecture that a high degree of physicochemical stereospecificity is exhibited by taste receptors.

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f_i^- R Factors giving Chloramphenicol Resistance

ALTHOUGH many f_i^+ R factors confer resistance to chloramphenicol, f_i^- R factors seldom do. Watanabe *et al.*¹ stated in 1964 that all the naturally occurring f_i^- R factors which they had studied lacked chloramphenicol resistance. In our laboratory, no f_i^- R factor giving chloramphenicol resistance has been observed among several hundred drug-resistant strains of enteric bacteria. In 1968 Watanabe, Furuse and Sakaizumi² reported an f_i^- R factor (S-a) from *Shigella* which conferred chloramphenicol resistance at about the same level as f_i^+ R factors. Aoki, Egusa, Ogata and Watanabe³ this year described R factors from the fish pathogen *Aeromonas liquefaciens*, which were all f_i^- and some of which carried chloramphenicol resistance determinants.

Watanabe⁴ found that factor S-a exhibited no superinfection immunity with any of several f_i^+ or f_i^- R factors.

We wish to report that S-a and two of Watanabe's R factors from *A. liquefaciens* carrying chloramphenicol resistance (our designations RA3 and RA4) constitute in *Escherichia coli* K12 a new compatibility group which we propose to call W (for Watanabe).

Factor S-a confers resistance to streptomycin (S), chloramphenicol (C), kanamycin (K) and sulphonamides (Su). Both RA3 and RA4 confer resistance to S, C and Su.

Evidence for the new compatibility group is presented in Tables 1 and 2. The W factors are not excluded by and can coexist stably with an F-like R factor, R136, an I-like R factor, R64 (ref. 5), the P-type factor, RP4 (ref. 6), N-type R factors, N3 and R46 (ref. 7) and two R factors from *A. liquefaciens*, RA1 and RA2, not at present assignable to any compatibility group. Transfer of a W factor was not inhibited by the presence of another W factor in the recipient, but, in every colony tested, led to the dislodgment of the resident factor. Thus surface exclusion, seen with other groups of plasmids, was apparently absent but even temporary coexistence was not demonstrated.

The two C-sensitive derivatives of J53(S-a) (Table 2) retained all other resistances (S, K and Su). One such J53 (S-aC^s) segregant was used as recipient in matings recorded in Table 1. All three factors of the W group lose resistance to chloramphenicol at a high rate. Thus, although all members of this group so far identified confer chloramphenicol resistance, the discovery of W factors without this marker may be predicted.

Since these R factors seem to constitute a group distinct from other R factors so far tested their resistance genes may perhaps have a different evolutionary origin. To test this we are trying to show whether they determine a chloramphenicol inactivating enzyme similar to that of *fi*⁺ factors^{8,9}. The kanamycin resistance of S-a is unusual. All other R factors examined in our laboratory, which determine kanamycin

Table 2 Stability of R Factors Singly and in Pairs

Strain	Resistance markers	Compatibility group	No. of colonies tested		
			Total	T ^a	C ^a
J53(S-a)	SCKSu	W	211	—	2
J53(RA3)	SCSu	W	181	—	1
J53(RA4)	SCSu	W	62	—	0
J53(R64)	ST	I	40	0	—
J53(N3)	STSu	N	152	0	—
J53(R46)	ASTSu	N	40	0	—
J53(RP4)	ATK	P	40	0	—
J53(S-a)(R64)		W+I	137	0	0
J53(Sa)(R46)		W+N	298	0	1
J53(S-a)(RP4)		W+P	849	0	1
J53(S-a)(RA1)		W+?	612	0	4
J53(RA3)(R64)		W+I	84	0	0
J53(RA3)(N3)		W+N	76	0	1
J53(RA3)(R46)		W+N	20	0	0
J53(RA3)(RP4)		W+P	20	0	0
J53(RA3)(RA1)		W+?	23	0	0
J53(RA3)(S-a)*		W+W	0	—	—
J53(RA4)(R64)		W+I	116	0	0
J53(RA4)(N3)		W+N	20	0	0
J53(RA4)(R46)		W+N	37	0	0
J53(RA4)(RP4)		W+P	148	0	1
J53(RA4)(RA1)		W+?	16	0	0
J53(RA4)(S-a)*		W+W	0	—	—

* No clones available to test (see Table 1).

resistance, confer a high level (> 500 µg/ml.) of resistance to kanamycin and also neomycin and paramomycin resistance, but not gentamicin resistance¹⁰. Such a pattern results from inactivation by phosphorylation^{11,12}. S-a gives low-level resistance to kanamycin (J53R⁻ is inhibited by 1 µg/ml., J53(S-a) by 20 µg/ml.), low level resistance to gentamicin (J53R⁻ is inhibited by 1 µg/ml., J53(S-a) by 5 µg/ml.) and none detectable to neomycin or paramomycin, a pattern which may result from inactivation by acetylation^{8,12,13}. It may be that this pattern of aminoglycoside resistance is unique to the W class.

Kanamycin used was 'Kantrex', kanamycin sulphate, from Bristol Laboratories Ltd. Gentamicin was 'Genticin', gentamicin sulphate from British Schering Ltd.

Note added in proof. Not all *fi*⁻ R factors determining chloramphenicol resistance belong to group W. R57b (Witchitz, J. L., and Chabbert, Y. A., *J. Antibiot.*, **24**, 137-139; 1971) and R387 (unpublished observation) are *fi*⁻, give chloramphenicol resistance and are compatible with S-a.

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Table 1 Transfer Frequency

Donor*	Recipient*	Compatibility of R factor in recipient	Transferred resistance (chloramphenicol)	Selection for Transferred resistance (chloramphenicol) and resident resistance (tetracycline† or kanamycin)
J62(S-a)	J53		10 ⁻³	—
J62(S-a)	J53(RA1)	A?	4 × 10 ⁻⁴	3 × 10 ⁻⁵
J62(S-a)	J53(RA2)	A?	8 × 10 ⁻⁴	4 × 10 ⁻⁵
J62(S-a)	J53(R64)	I	10 ⁻³	10 ⁻⁴
J62(S-a)	J53(R46)	N	4 × 10 ⁻⁴	5 × 10 ⁻⁵
J62(S-a)	J53(N3)	N	10 ⁻⁴	10 ⁻⁵
J62(S-a)	J53(RP4)	P	5 × 10 ⁻⁴	5 × 10 ⁻⁵
J62(RA3)	J53		2 × 10 ⁻³	—
J62(RA3)	J53(RA1)	A?	9 × 10 ⁻⁴	8 × 10 ⁻⁴
J62(RA3)	J53(RA2)	A?	2 × 10 ⁻³	4 × 10 ⁻⁴
J62(RA3)	J53(R64)	I	2 × 10 ⁻³	5 × 10 ⁻⁴
J62(RA3)	J53(R46)	N	2 × 10 ⁻³	10 ⁻⁴
J62(RA3)	J53(N3)	N	8 × 10 ⁻⁴	10 ⁻⁴
J62(RA3)	J53(RP4)	P	2 × 10 ⁻³	3 × 10 ⁻³
J62(RA3)	J53(S-a)	W	2 × 10 ⁻³ ‡	0
J62(RA3)	J53(R136)	F	10 ⁻³	2 × 10 ⁻⁴
J62(RA4)	J53		10 ⁻³	—
J62(RA4)	J53(RA1)	A?	2.5 × 10 ⁻³	10 ⁻³
J62(RA4)	J53(RA2)	A?	2 × 10 ⁻³	9 × 10 ⁻⁴
J62(RA4)	J53(R64)	I	4 × 10 ⁻³	7 × 10 ⁻⁴
J62(RA4)	J53(R46)	N	2 × 10 ⁻³	2 × 10 ⁻⁴
J62(RA4)	J53(R15)	N	10 ⁻³	—
J62(RA4)	(RP4)	P	4 × 10 ⁻³	2 × 10 ⁻³
J62(RA4)	(S-aC ^s)	W	2 × 10 ⁻³ +	0
J62(RA4)	(R136)	F	5 × 10 ⁻³	5 × 10 ⁻⁴

* J62 and J53 are nutritionally distinguishable strains of *Escherichia coli* K12 F⁻.

† Counts on tetracycline-containing plates are generally lower than on plates without tetracycline, even when all bacteria in the inoculum carry genes for tetracycline resistance.

‡ 50 recipient colonies tested. In all, the transferred R factor was present, the previously resident one was lost.

Compatibility Groups among fi^- R Factors

TRANSMISSIBLE R factors in bacteria are divisible into two main classes, fi^+ (fertility inhibition⁺) and fi^- , according to their effect on F mediated conjugation¹. fi^+ R factors determine F-like pili². Some fi^- R factors determine pili similar to those specified by col I (I-type pili)³ which can be recognized as receptors for I-specific phages like If1 (ref. 4). Although heterogeneity among fi^- R factors has already been indicated⁵⁻⁸, it is sometimes assumed that all fi^- R factors have I pili^{9,10}.

Among 26 fi^- R factors examined by Lawn *et al.*², twenty determined the production of I-type pili. Strains of *Escherichia coli* K12 carrying the other six R factors (of which one example was R46) permitted no increase of I-specific phage If1 and so by this criterion give no evidence of having I-type pili. We find that the classical fi^- factors, N3 and R15 (ref. 1), also fail to allow multiplication of I-specific phage. Other examples of fi^- R factors which do not allow multiplication of I-specific phage in *E. coli* K12 are RP4, derived from a strain of *Pseudomonas aeruginosa*¹¹, and S-a^{12,13}.

One of the ways in which plasmids are classified is by superinfection immunity: bacteria carrying one plasmid hinder the entry of others of the same group (surface exclusion) and also two plasmids of the same group will not coexist stably in the same host (incompatibility)¹⁴.

By these criteria, most fi^+ R factors constitute one class of plasmid. These also characteristically produce pili similar to those of the sex factor F. By the same criteria the fi^- plasmids are heterogeneous. Those which determine I pili constitute one superinfection immunity class. N3, R15 and R46 belong to another which we propose to call N. RP4 represents a third¹¹ and S-a a fourth¹³.

Table 1 Frequency of Transfer

Donors	Resistance markers	Recipients	Compatibility group of resident R factor	
J62(R144-3)	K	J53		2.7
		J53(R64)	I	$0 (< 10^{-7})$
		J53(R46)	N	4.6
		J53(N3)	N	1.1
J62(R64)	ST	J53		1.8×10^{-3}
		J53(R44)	I	$0 (< 10^{-7})$
		J53(R46)	N	1.5×10^{-3}
		J53(RP4)	P	1.8×10^{-3}
J62(RP4)	ATK	J53		3.3×10^{-3}
		J53(R144)	I	1.4×10^{-2}
		J53(R64)	I	3.0×10^{-3}
		J53(R46)	N	1.4×10^{-3}
J62(N3)	STSu	J53(N3)	N	2.4×10^{-3}
		J53		2.2×10^{-3}
		J53(R144)	I	3.0×10^{-3}
		J53(R46)	N	7.2×10^{-5}
J62(R46)	ATSu*	J53(RP4)	P	3.8×10^{-3}
		J53		2.1×10^{-3}
		J53(R44)	I	3.3×10^{-3}
		J53(N3)	N	2.2×10^{-5}
		J53(RP4)	P	2.0×10^{-3}

The frequency of transfer is expressed as the number of R+ recipients after 1 h at 37° C/No. of R+ donors.

A, Ampicillin; S, streptomycin; T, tetracycline; K, kanamycin; Su, sulphonamide.

* R46 carries resistance to ASTSu but in these experiments a spontaneous, non-reverting segregant, giving no resistance to streptomycin, was used.

The evidence for their division into classes is shown in the tables. Table 1 shows the frequency of transfer of R factors of groups I (R144-3 and R64), N (N3 and R46) and P (RP4) to recipients with or without resident R factors. Selection was

made with antibiotic to which the donor, not recipient, was resistant. Where colonies developed, they were subcultured, and tested for the continued presence of all markers of both factors. After growth in drug-free broth, the stability of markers of each R factor was examined by replica plating or, sometimes, by streaking out individual colonies (Table 2). Watanabe demonstrated surface exclusion in matings between strains carrying R15 and N3, but did not test for their stable coexistence. Since N3 determines resistance to streptomycin, tetracycline and sulphonamides, while R15 determines streptomycin and sulphonamide resistance, one cannot directly demonstrate the existence of R15 in the presence of N3. We transferred N3 to K12(R15), selecting for tetracycline resistance; we used the recombinant strains as donors in matings with recipients, selecting for streptomycin resistance, and screened the recombinants for tetracycline resistance. From two of the donor strains, all recombinants tested were tetracycline resistant, while from the third, most (fifty-seven out of sixty-three) were tetracycline-sensitive. This suggests that the two factors do not coexist stably.

Table 2 Stability of R Factors Singly and in Pairs

Strain	Resistance markers	Total replicated	No. of colonies				
			No growth	A	S	T	K Su
J53(R144)	K	50	—	—	—	—	0
J53(R64)	ST	1,000	—	—	0	—	—
J53(RP4)	ATK	217	—	—	—	0	0
J53(R46)	ATSu	132	1	—	—	1	—
J53(N3)	STSu	817	—	—	0	2	—
J53(R144)(R64)		0	—	—	—	—	—
J53(R64)(RP4)		1,298	—	—	0	—	0
J53(R144)(R46)		226	7	—	—	7	2
J53(R144)(N3)		2,267	—	—	2	—	0
J53(RP4)(R46)		281	—	—	—	—	0
J53(RP4)(N3)		102	1	0	—	1	1
J53(R46)(N3)		144	93	50	—	—	—

Abbreviations are as in Table 1.

* One strain had lost RP4 and T^R from N3.

The tables show that exclusion of one I-like factor by another is complete, whereas with the N group of plasmids, frequency of transfer to a host already carrying a related plasmid is reduced about 100-fold or less¹. Coexistence, however, does not last through many generations, and the plasmid which is most frequently retained is that whose resistance marker has been selected in the cross. Growth in drug-free medium leads to symmetrical loss, about half the clones retaining each one.

Guerry and Falkow (personal communication), in studying R factor homology by DNA hybridization, found that N3 shows no measurable homology with the I group factors R64, R144 or col I nor with any fi^+ plasmid. Khatoon and Iyer⁸ have isolated a new sex factor specific phage, whose indicator strain carries a naturally occurring, derepressed R factor RM98. Strains carrying R46 or N3 propagate this phage but strains with F or I pili so far tested do not (Iyer, personal communication), so it seems likely that the N group of plasmids determine specific pili (or other surface structure) different from F or I pili.

Some confusion has arisen because those fi^- R factors most studied in Japan¹ belonged to the N group, and those studied most extensively in England² were I-like plasmids.

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Quantitative Method for assessing One Symptom of the Withdrawal Syndrome in Mice after Chronic Morphine Administration

FEW quantitative methods exist for assessing the effects of withdrawing morphine from addicted laboratory animals. The aim of the experiments described here was to assess whether a method which depends on the number of characteristic vertical jumps made by mice after morphine withdrawal¹ could be used as a measure of the withdrawal syndrome. This simple method has now been found to give reasonably repeatable and consistent results.

If nalorphine, a narcotic antagonist, is injected into mice which have been chronically injected with morphine, it precipitates a withdrawal syndrome which includes hypermotility, tremors, diarrhoea, micturition and piloerection². The "intensity" of the syndrome was rated by Huidobro and Maggiolo on a five-point scale, but each point on their scale comprised a number of different symptoms which varied in frequency and intensity in different mice³. Recently Way and his colleagues reported a simple quantal method; they determined the proportion of mice which leapt off a raised platform during 15 min after the injection of the antagonist naloxone⁴. With our method, which was developed independently, a measure of frequency, instead of an all-or-none measure, can be obtained from each mouse, and an 8 min observation period has been found adequate for most purposes.

More than 300 female mice of a T.O. strain (18–22 g) were used; injections were subcutaneous and doses are expressed in mg/100 g body weight throughout.

In the first experiment morphine sulphate was injected once daily at 1000 h; 1 mg was given on the first day, and this was increased by 1 mg daily. After 4 days of injections the mice were divided into three groups. Group 1 received 4 mg/day for the rest of the experiment. In group 2 the dose continued to be increased by 1 mg/day and in group 3 it was increased by 4 mg/day (Fig. 1a). To precipitate a withdrawal syndrome, nalorphine (1 mg) was injected into eight mice from each group 5 h after the daily morphine administration. The mice were then placed singly in enclosed rectangular (12 × 8 × 15 cm) 'Perspex' containers. The number of jumps made by each mouse was counted in an 8 min period which began 3 min after the nalorphine injection. A "jump" was defined as any response by a mouse in which all four feet were off the ground at the same time. Vigorous vertical jumping usually began about 3 min after the injection of the antagonist. Mice were only used once and the results are shown in Fig. 1b.

There were marked differences between the mean scores of the three groups, though there were also considerable individual differences within each group. In group 1 the number of jumps remained at the low level reached after the fourth injection. The distribution of scores was, however, markedly skewed because some mice did not jump at all. Non-parametric statistical tests were therefore used throughout⁵. Group 2 jumped significantly more often (Mann-Whitney U-test: $P < 0.01$) than group 1 after both 8 and 10 days. The results from groups 2 and 3 show that by day 8 a greater number of jumps occurred ($P < 0.001$) in group 3, whose dose was increased more rapidly, than in group 2. It seems that where the dose is increased by an equal amount daily the intensity of the precipitated jumping is proportional to the amount of morphine injected.

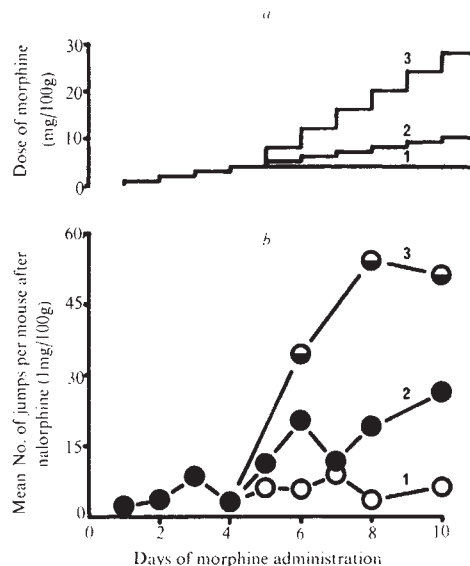


Fig. 1 The intensity of the withdrawal syndrome in mice given one daily injection of morphine. *a*, The ordinate shows the dose of morphine given at each injection (mg/100 g). All mice received morphine on a regime increasing by 1 mg/100 g (from 1 mg/100 g) for the first 4 days. Then group 1 continued to receive 4 mg/100 g at each injection; group 2 had the dose increased by 1 mg/100 g/day; group 3 increased by 4 mg/100 g/day. *b*, The effect of these different dose regimes on the average number of jumps over 8 min in groups of eight mice. Jumping was precipitated by 1 mg/100 g of nalorphine. Group 1 (○) remained at a low level of jumps. Group 2 (●), with a small dose increment, jumped more than group 1 but less than group 3 (●), the latter having a higher dose increment.

In other experiments morphine was injected three times daily (0900 h, 1300 h and 1700 h). Group 1 received 5 mg at each injection. Group 2 was given doses of 5, 5 and 7.5 mg of morphine in the first three injections and each of these was then increased by 2.5 mg/day. The higher dose at the third daily injection was to minimize any overnight withdrawal effects. Control animals received saline three times daily. Jumps were then counted after an injection of nalorphine, as before.

Fig. 2 shows that initially there was a rise in the number of jumps produced in both groups 1 and 2. Significant differences ($P < 0.05$) were obtained between control and morphine-treated mice from the second day of the experiment onwards. After 4 days (twelve injections) group 1, which was receiving a constant dose of morphine, made fewer jumps while group 2, which was on an increasing dose schedule, continued to show an increase in jumps. It was therefore not possible to obtain a consistent quantitative relationship between the number of jumps and the total dose when a constant amount of morphine was injected.

These results suggest that to obtain an increase in the severity of the withdrawal syndrome, as reflected in the number of jumps, morphine must be injected on an increasing dose schedule.

To confirm that the jumping which occurred in the precipitated abstinence syndrome was due to drug withdrawal, another group of mice which had received morphine three times daily for 4 days merely had their injections stopped but no antagonist was given. Jumping again occurred with a maximum between 14 and 24 h after the last morphine injection. Greater variability was seen during the abstinence syndrome compared with the antagonist precipitated withdrawal syndrome.

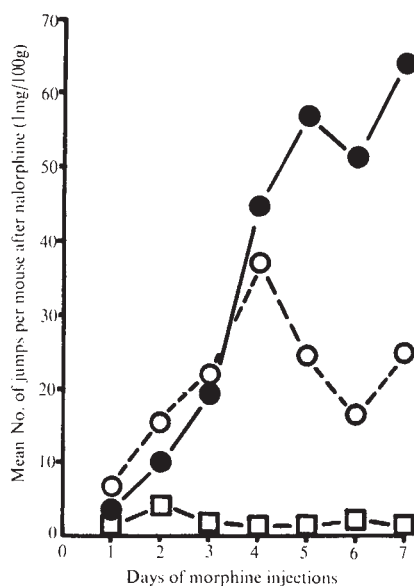


Fig. 2 The effect of a constant or increasing dose regime and the intensity of the withdrawal syndrome in mice given morphine three times daily. The ordinate shows the mean number of jumps, following an injection of nalorphine (1 mg/100 g) in groups of eight mice over 8 min. Group 1 (○) received 5 mg/100 g morphine at each injection and at first the number of jumps increased but later fell. Group 2 (●) was injected with morphine on an increasing dose schedule (see text) and the average number of jumps continued to increase throughout the experiment. Little jumping was seen in control mice given saline three times daily (□).

Jumping has also been correlated with other forms of behaviour following the withdrawal of morphine from mice. For example, the number of jumps seems to be positively correlated with faecal output in the nalorphine-induced abstinence syndrome. This result is in agreement with work using morphine-addicted rats⁶. A decrease in body weight is one sign of morphine withdrawal in rats⁷⁻⁹, but has not been observed in mice¹⁰. In mice injected as our group 2, however, a body weight loss does occur on discontinuation of morphine treatment. This is positively correlated with the time course of jumping during the abstinence syndrome.

This method of looking at the number of jumps made by each mouse following the precipitation of a withdrawal syndrome by a narcotic antagonist enables differences between regimes of morphine administration to be detected using small groups of animals. If groups of mice are given the same morphine treatment but, for example, different pretreatments, the effects of the latter on the number of jumps can also be investigated. Thus the method can be used to study quantitative aspects of the development of physical dependence on morphine¹¹. Second, the number of jumps might be used as an index of the addiction liability of a new drug. It could also be used to determine whether a drug can prevent an abstinence syndrome in morphine treated mice.

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Verbal Communication with L-Dopa Treatment

DURING the past 2 years we have studied the action of L-dopa in drug-induced Parkinsonism¹, true Parkinsonism² and psychosis³. In all investigations we found numerous behavioural aberrations. Here, however, we discuss the beneficial effect of L-dopa on verbal communication.

Placebo was given for 1 week and then replaced by oral L-dopa for 2 weeks, in a dose of 1 g in the first week and 2 g in the second week. All patients remained on their previous neuroleptic medication throughout the study to yield a reliable and steady behavioural base line. Ten of the original fourteen patients were given the Kent-Rosanoff word association test. (The four patients excluded were deficient in the English language.) Response time and the responded word were recorded immediately after the stimulus word was presented. If the patient's response was in the top 75% of the frequency

Table 1 Verbal Communication as Total Percentage

Patient	Neuroleptic medication	1 g of L-dopa	2 g of L-dopa
A.B.	88.8	92.5 †	92.5 †
R.D.	22.2	25.9 †	25.9 †
C.E.	77.7	81.4	88.8 †
M.G.	37.0	44.4 †	40.7
R.H.	66.6	81.4 †	74.0
N.L.	77.7 †	74.0 *	77.7 †
W.M.	70.3	81.4	88.8 †
T.O.	62.9	81.4 †	81.4 †
J.P.	70.3	88.8 †	81.4
R.W.	44.4	59.0	70.3 †

$P=0.011$. * Hallucinated when tested. † Highest score patient obtained through study.

Table 2 Communication Response Time in Seconds

Patient	Neuroleptic medication	1 g of L-dopa	2 g of L-dopa
A.B.	1.5	1.3	1.2*
R.D.	4.6	2.0	1.9*
C.E.	2.4	2.0	1.4*
M.G.	4.7*	5.1	5.9
R.H.	4.1	1.9	1.5*
N.L.	2.8	2.1	1.9*
W.M.	3.0	2.8	2.2*
T.O.	2.9	2.3	1.8*
J.P.	2.1	1.7	1.6*
R.W.	1.2*	1.2*	2.0

$P=0.055$. * Fastest response time for patient through study.

table for the presented stimulus word, it was considered communicable. Finally, all responses were added to yield a total of communicable and noncommunicable responses and their percentages were calculated.

Nine patients significantly improved verbal communication with L-dopa treatment (binomial test, $P=0.011$); there was an optimal dose for some. No significant difference was obtained for the 1 and 2 g doses when individually compared for improvement and only three patients communicated best for both doses. The patient whose communication did not improve with L-dopa treatment was observed to hallucinate while receiving L-dopa. Verbosity in all patients improved to the extent that some spontaneously reported their hallucinations.

Eight patients responded to stimulus words faster when L-dopa was administered, and two responded slower (binomial test, $P=0.055$), and when the 1 g and 2 g doses are compared the fastest and slowest scores all occur with 2 g (binomial test, $P=0.001$). The two patients who responded more slowly with L-dopa treatment, however, improved their verbal communication.

It is known that dopamine and noradrenaline, for which dopa is the precursor, resemble stimulant drugs in their action. These catecholamines are located in the brain stem at the sites of action of the stimulant drugs, such as amphetamine. L-Dopa may thus stimulate the lethargic, withdrawn patient. Improved verbalization may be helpful in the psychotherapy of noncommunicative patients: we have therefore initiated a preliminary trial of L-dopa in autistic patients.

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Drug Use and Grades in College

ONE of the most compelling arguments against illegal drug use, especially by the young, is that it instills in the user an "amotivational syndrome" of apathy, lethargy and loss of motivation in the conventional sense¹. The argument assumes

that drug use tends to become routine and that the drugs specifically prohibited by law are associated with reduced achievement-oriented behaviour. Given the fact that drug use is currently at an all-time high among the young—and possibly more so among society's talented young than in any other group—these issues deserve empirical exploration. The latest Gallup poll, conducted in December 1970, indicated that in a roughly random sample of American college students, 42% had tried marijuana at least once. Moreover, this was an increase of almost 1% per month from previous surveys.

During January and February 1970, I distributed a brief questionnaire to about 560 students attending my deviance and delinquency classes at the State University of New York at Stony Brook. Since these classes are not representative of the student composition of the university of which they are a part, I regard these data as exploratory rather than definitive. About seven students in ten had smoked marijuana at least once in the preceding 6 months. Roughly three in ten had used an amphetamine in the preceding 6 months to become "high"; this was the second most popular drug taken. Heroin was one of the least often tried or used drugs in the survey, with only 4% of the students taking it at least once in the preceding 6 months. But these figures exaggerate the importance of all drugs apart from marijuana because they were chiefly used on a very episodic and experimental basis. Roughly 85–90% of all recorded episodes of drug use reported by the sample involved marijuana alone and only slightly more than one instance in ten of illegal drug use involved the combined use of any and all drugs apart from marijuana. It is therefore misleading to discuss the drugs used on the college campus as if they were used with equal frequency. The phenomenon is chiefly one of marijuana use.

The median level of marijuana use was 1.0 times per week. Since the average length of a marijuana "high", or intoxication, is about 3 h, the typical user is under the influence of this drug for roughly 4 h per week, that is, 3–4% of his waking hours. It is therefore difficult to imagine how marijuana could generate a significant loss in motivation, given its relatively small space in the typical user's temporal life, unless the recent studies, which indicate that drugs containing THC may have long term effects, are taken into account².

After making the crude distinction between the total abstainer and the student who had used marijuana once or more, I found that their grades were almost identical: 32% of the marijuana experimenters and 33% of the total abstainers had a "B" grade point average or better. This is obviously well within the range of random fluctuation, but a more detailed analysis of users yields an interesting relationship obscured by the gross dichotomization between the user and the non-user. There seems to be a curvilinear relationship between marijuana use in the preceding 6 months and grades earned. The highest grades were earned by the casual and infrequent marijuana smoker, and the lowest by the heaviest user; the abstainer earned only slightly higher grades than the heavy user. Only 29% of the daily marijuana users had achieved a B average or better, and 31% of the abstainers did as well. But 45% of those smoking three or four times a month and 47% of those smoking once or twice a month had the same average (Table 1).

If the number of drugs the student experiments with at least once in his lifetime is used as another indicator of drug involvement, there seems to be no difference between the grades of the abstainer and those of the student who has tried, at least once, between one and three drugs. But grades decreased significantly when I examined the student who had tried four or more different kinds of drug. There were 10% fewer students with a B average or better in this group (Table 2).

The same result is obtained when specific drugs are used as a measure of drug involvement. Only 12% of the heroin experimenters (those students who have tried heroin once or more in their lives, a category which includes addicts), the lowest percentage of any group, had a B average or better, while 32% of the total sample, 32% of the abstainers and 32% of mari-

Table 1 Average Grades by Frequency of Smoking Marijuana in Preceding 6 Months

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
Every day	29	35	35	99	31
3-6 times/week	24	40	36	100	58
1-2 times/week	23	43	34	100	88
3-4 times/month	45	27	27	99	51
1-2 times/month	47	32	21	100	57
Less than once per month	31	50	19	100	48
Never	31	43	25	99	157

Table 2 Average Grades by Total Number of Different Drugs Ever Tried (or "Experimented With") in One's Lifetime

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
None	32	44	24	100	140
One	36	39	26	101	160
Two or three	35	42	24	101	110
Four or more	24	37	39	100	103

juana smokers obtained a B average. Of those who had taken cocaine or methedrine, only 17% obtained a B average or better. Thus it seems that the harder drugs are associated with low grades but that marijuana has no impact at all on grades. Nearly all heroin, cocaine and methedrine experimenters had tried a wide range of other types of drug, but marijuana users varied in their involvement with other drugs—from using none to using nearly all available drugs—and so they represent the broad spectrum as regards grades as well. Marijuana users as a whole have average grades (Table 3).

Table 3 Average Grades by Ever Tried Various Drugs at Least Once in One's Lifetime

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
Total sample	32	41	27	100	561
Total abstainer	32	44	24	100	140
Marijuana	32	40	28	100	360
Opium	31	47	22	100	36
Mescaline	29	38	33	100	115
Amphetamines	28	39	34	101	116
LSD	22	40	39	101	96
Barbiturates	22	41	36	99	58
Cocaine	17	62	21	100	29
Methedrine	17	53	31	101	36
Heroin	12	65	24	101	17

The original curvilinear relationship between marijuana use and grades seems applicable to various groups and social categories. It holds for men and women considered separately, for upper-classmen, freshmen and sophomores, and for students from all social classes. The break in grades came at the point at which marijuana was used weekly or more. Of those smoking marijuana less than once a week there was a higher percentage with a B average or better compared with the abstainers, the difference being just over 7%. The abstainer was more likely than the student smoking once a week or more to have a B average, the difference here being less than 7% (Tables 4-6).

Table 4 Average Grades by Marijuana Use in Preceding 6 Months, holding Sex Constant

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
Men					
Never	21	42	37	100	62
Less than weekly	31	40	29	100	80
Weekly or more	15	44	41	100	111
Women					
Never	39	43	18	100	95
Less than weekly	47	37	15	99	99
Weekly or more	41	37	22	100	63

Table 5 Average Grades by Marijuana Use in Preceding 6 Months, holding Class in College Constant

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
Juniors and seniors					
Never	35	45	21	101	78
Less than weekly	39	40	21	100	98
Weekly or more	22	47	31	100	68
Freshmen and sophomores					
Never	30	44	26	100	73
Less than weekly	42	37	22	101	79
Weekly or more	26	36	37	99	107

Table 6 Average Grades by Marijuana Use in Preceding 6 Months, holding Father's Occupation Constant

	Straight B or higher	C+ to lower than B	Lower than C+	Total %	N
Professional and executive					
Never	39	39	22	100	54
Less than weekly	53	35	12	100	66
Weekly or more	31	36	34	101	59
Sales and clerical					
Never	31	40	29	100	52
Less than weekly	38	40	22	100	63
Weekly or more	23	42	35	100	77
Manual labour					
Never	26	48	26	100	46
Less than weekly	28	35	38	101	40
Weekly or more	17	44	39	100	36

These data suggest that the amotivational syndrome is far from inevitable—or even typical—in illegal college drug use and that it may be associated only with heavy drug use. But the data do not show whether the relationship between grades (as a measure of achievement) and drug use is a biochemical, a psychological or a sociocultural phenomenon, or whether drug users in college are a preselected group as regards academic potential; some minimal degree of drug use could conceivably lower their grades to the level of their less talented abstaining peers. Moreover, the data do not show whether the relationships described and analysed here have any relevance for very different populations such as the very young, or residents of slum areas.

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¹ McGlothlin, W. H., and West, L. J., *Amer. J. Psychiat.*, **125**, 372 (1968).

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Morphological and Cytochemical Effects of Marijuana Cigarette Smoke on Epithelioid Cells of Lung Explants from Mice

THERE have been many experimental studies on the chemical constituents responsible for the hallucinogenic effects of marijuana^{1,2}, but we know of no reports on the biological effects of marijuana cigarette smoke on the respiratory tract. We have been interested for some years in the biological effects of fresh cigarette smoke, particularly its role in malignant transformation in the respiratory tract of intact animals³ and in cultured lungs⁴. We have now compared the effects of smoke from cigarettes with and without marijuana.

We used the model system developed for exposing lung explants to puffs of fresh cigarette smoke in standardized conditions^{5,6}. Lung explants from Snell's and C57BL mice were prepared on coverslips and exposed in a Filtrona CSM12 smoking machine to puffs of fresh cigarette smoke. Cigarettes were prepared with tobacco alone and with the same tobacco mixed with marijuana (0.5–1 g) in a powder form. We used two types of marijuana, one containing 0.4% tetrahydrocannabinol (THC) and one containing 4% THC. Altogether experiments were carried out on more than 400 lung explant cultures. For each experiment a minimum of eight sets consisting of twenty-four coverslips with matched lung explants was used. Each set comprised a control culture not exposed to cigarette smoke, a culture exposed for 5 consecutive days to two puffs (8 ml. at intervals of 58 s) of cigarette smoke without marijuana, and a culture exposed in the same manner to two puffs of fresh cigarette smoke with marijuana. Media were changed immediately after each exposure with the exception that, after the fifth exposure, media were changed only

after 1 h. Cytological characters and chromosomal behaviour during mitosis were studied in live cultures under phase contrast, and in the original unsquashed stained cultures 6–240 h after exposure. The mitotic index expressed as a percentage was obtained by counting all mitotic figures and relating them to the total number of cells of each monolayer grown on the coverslip. DNA metabolism was examined by autoradiography and Feulgen microspectrography^{5–7}. All results were reproducible, and were the same for lung cultures from Snell's and C57BL mice.

There were differences between control cultures and those exposed to cigarette smoke with and without marijuana (Table 1). Cigarette smoke alone was cytotoxic⁴ after four puffs, while cigarette smoke with marijuana had little cytotoxicity (Table 1) perhaps because after the addition of marijuana, which is a sticky resin, the cigarette smoke had a larger side-stream, so that less smoke *per se* reached the culture. After 24–48 h of exposure to ten puffs of marijuana cigarette smoke, the shape of epithelioid cells and nuclei was affected. After exposure to cigarette smoke alone, these characters were rarely different from those of controls (Fig. 1a and b), but after exposure to marijuana cigarette smoke, a considerable number of nuclei were unusually large with large nucleoli, which were often in close proximity to each other (Fig. 1c), and had a tendency to fuse. Furthermore, although in control cultures and cultures exposed to cigarette smoke alone, the outgrowing epithelioid cells formed a monolayer showing respectively more or less contact inhibition (Fig. 1a and b), there was a marked tendency to criss-cross formation and piling up of cells after exposure to marijuana cigarette smoke. This indication of abnormal proliferation was accompanied by an increase of mitotic index and by stimulation of DNA synthesis. Although the increase in mitotic index after exposure to cigarette smoke alone was not statistically significant compared with that of the controls, that after exposure to marijuana cigarette smoke was, compared with both controls ($P=0.0005$) and cultures exposed to cigarette smoke alone ($P=0.025$). Lagging of chromosomes in metaphase and anaphase was relatively frequent after exposure to marijuana cigarette smoke (Fig. 1d). A further detailed chromosomal analysis is planned to see whether marijuana cigarette smoke evokes chromosomal abnormalities in the epithelioid cells of the lung explant. The increase of nuclear sizes after marijuana cigarette smoke was accompanied by a marked increase in DNA content of the epithelioid cells. While in control cultures even the largest nuclei (which, because of their scarcity, had to be sought) contained only rarely 4 DNA ($\text{ratio } \frac{2\text{DNA}}{4\text{DNA}} = \frac{10}{1}$), cultures exposed to cigarette smoke without and with marijuana had a higher frequency of nuclei with 4 DNA. Although the

Table 1 Comparison of Effects of Fresh Smoke from Cigarettes without and with Marijuana (0.4% Tetrahydrocannabinol) on Morphology, Mitotic Index and DNA Synthesis in Epithelioid Cells of Lung Explants from Snell's and C57BL Mice

Type of experiment	Cytotoxic effects	Abnormalities in size and shape of cells	Mitotic index ($n_1=54$)	DNA content (Feulgen microspectrography) ($n_2=450$) Mean ratio of frequency of nuclei $\frac{2\text{ DNA}}{4\text{ DNA}}$	DNA synthesis ($^3\text{H-TdR}$) ($n_1=15$) Frequency of labelled cells
Control	0	0	0.28 ± 0.07	$\frac{10}{1}$	10.9 ± 2.1
Cigarette smoke without marijuana	++	(+) - +	0.39 ± 0.002	$\frac{8}{1}$	13.6 ± 2.6
Cigarette smoke with marijuana	(+)	++	0.6 ± 0.11 $p_{\text{Co}}=0.0005$ $p_{\text{Ci}}=0.025$	$\frac{2}{1}$ $p=0.0005$	19.2 ± 1.9 $p_{\text{Co}}=0.01$ $p_{\text{Ci}}=0.05$

(+), Doubtful; (+) - +, slight effect; ++, pronounced effect.
 n_1 , Number of cultures examined; n_2 , number of cells measured.

ratio $\frac{2 \text{ DNA}}{4 \text{ DNA}}$ of $\frac{8}{1}$ found after exposure to cigarette smoke alone was not statistically significant compared with that of the controls, there was a striking increase in nuclei with 4 DNA after exposure to marijuana cigarette smoke, resulting in a ratio $\frac{2 \text{ DNA}}{4 \text{ DNA}}$ of $\frac{2}{1}$, which was highly statistically significant.

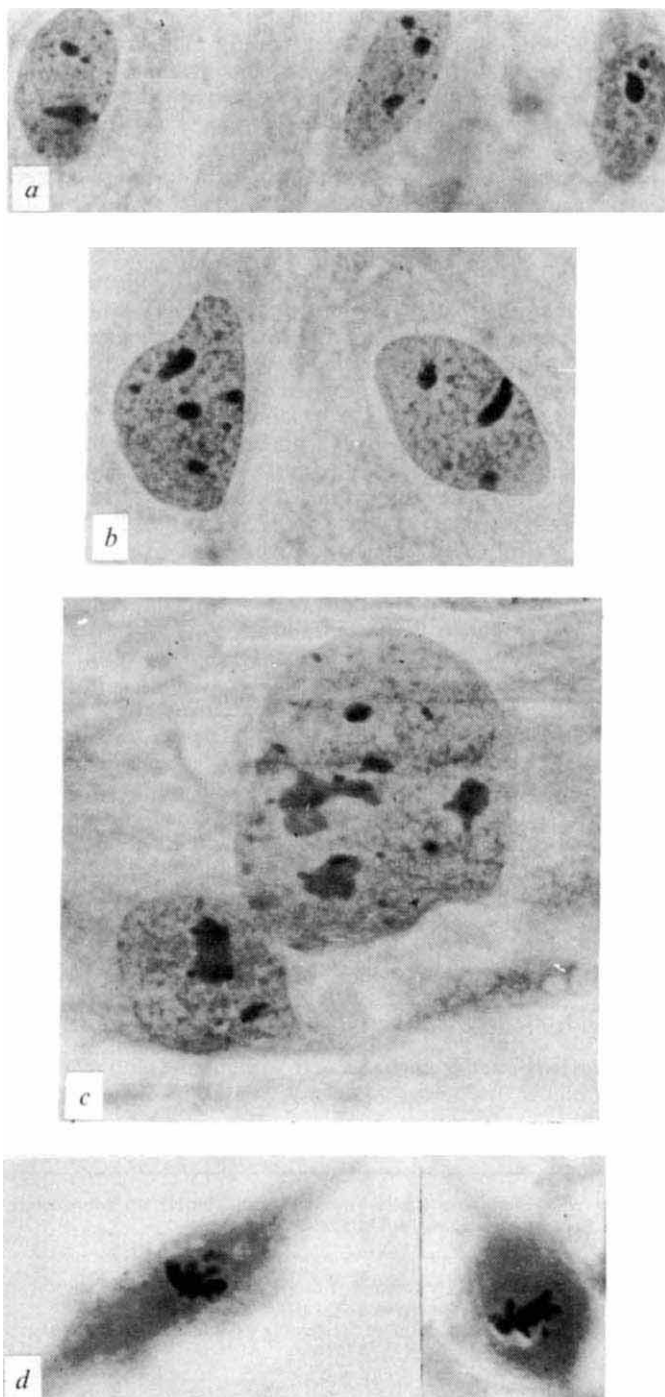


Fig. 1 *a*, Epithelioid cells in monolayer of 15 day old Snell's mouse lung explant, stained with haematoxylin and eosin. Note well separated uniform nuclei ($\times 1,000$). *b*, The same culture as in *a*, but 72 h after five exposures to two puffs of cigarette smoke without marijuana. Note larger and more irregular nuclei than in *a*. *c*, The same culture as in *b*, but 72 h after five exposures to two puffs of cigarette smoke with marijuana (0.4% THC). Note larger and more irregular nuclei than in *b*. Note also close proximity of nuclei, suggesting fusion. *d*, Metaphases of epithelioid cells in 14 day old C57BL mouse lung explant, 72 h after five exposures to two puffs of cigarette smoke with marijuana. Note lagging of chromosomes.

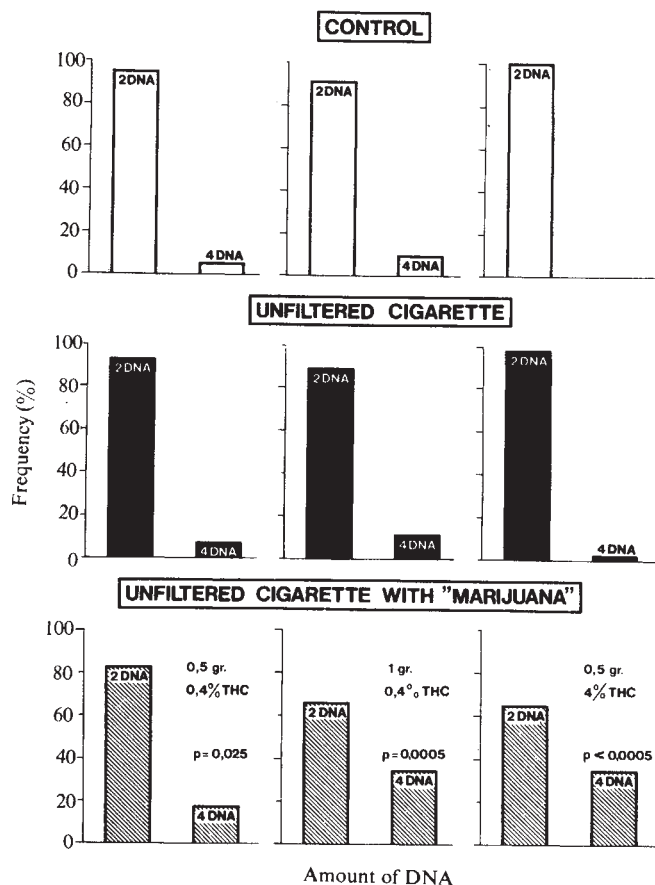


Fig. 2 Comparison between effects of fresh smoke (two puffs daily for 5 days) from one unfiltered cigarette, with and without different doses of marijuana and THC, on the DNA content of epithelioid cells ($N_1 = 1,200$) from lung explants of Snell's mice ($n_2 = 3$). n_1 = number of cells measured; n_2 = number of experiments. DNA content was determined by Feulgen microscopy.

A greater effect of cigarette smoke with marijuana than that of cigarette smoke without marijuana was also noted when DNA synthesis was studied by incorporation of tritiated thymidine ($^3\text{H-TdR}$). Although after cigarette smoke without marijuana the increase in frequency of labelled epithelioid cells was not statistically significant compared with that of controls, the augmentation in frequency of labelled cells after cigarette smoke with marijuana was statistically significant.

It thus seems that the addition of marijuana to cigarettes produces a smoke which evokes morphological and cytochemical alterations in epithelioid cells of lung explants, such as atypism, mitosis and DNA synthesis, to a significantly higher degree than does smoke from cigarettes without marijuana. Whether the effect of marijuana is due to THC, which is responsible for the hallucinogenic effect, cannot be decided at present. This needs further study on lung cultures with THC itself. Nevertheless our observation, that increasing concentrations of THC in marijuana cigarette smoke evoked earlier and more marked alterations, including higher DNA content, suggests that THC is at least partly responsible for the alterations. When lung explants were exposed to smoke from cigarettes with 4% THC marijuana, the number of epithelioid cells with 4 DNA was seventeen times greater than after exposure to cigarette smoke without marijuana (Fig. 2). On the other hand, when lung explants were exposed to smoke from cigarettes with 0.4% THC marijuana only, the number of 4 DNA cells was only two to three times greater than after exposure to cigarette smoke alone. Regardless of whether THC or other cannabinoids are directly involved, the finding that cytological and cytochemical alterations evoked by

cigarette smoke were intensified when marijuana was added is noteworthy. These data are of special interest in the light of reports that users of marijuana in Western countries, such as the United States, prefer smoking marijuana cigarettes to eating marijuana itself^{1,2}.

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Biological Level of Organization of the Chesowanja Robust Australopithecine

A PARTIAL cranium of an australopithecine has been described by Carney, Hill, Miller, and Walker¹ from Chesowanja in Kenya, a new Pleistocene locality which has been dated between 1.1 and 1.2 million years. The explicit statement, both written and in the reconstructions in this report, that the Chesowanja cranium is a large brained robust australopithecine—an evolutionary novelty as far as the robust lineage is concerned—is of considerable importance. I interpret the evidence differently.

My discussion here of the skull is within the descriptive framework provided by Carney *et al.* As these authors correctly recognized, the Chesowanja cranium (KNM-CH-1) shows unmistakable signs, both in its facial construction and in its dental morphology, that it is closely related to the robust australopithecines of Swartkrans, Kromdrai, Olduvai, and other African localities. Before discussing the morphology and the inferred functional interpretation of the cranium, I would like to list briefly the preserved parts of KNM-CH-1. Although it is not mentioned in Carney *et al.*'s report, in addition to the small frontal fragment, the partial cranium was found in two large pieces several feet apart. These two parts are the top of the right face which includes the crushed orbit and the maxillary part of the face which includes the right dentition without the incisors. The specimens were fitted and glued together, and the missing parts were replaced with a white filler. Carney *et al.* state that on the specimen: "Distortion is slight and consists chiefly of folding of the right orbital plate by lateral pressure, and slight flexion of the hypophyseal fossa that is probably associated with this deformation. . . . The base of the cranium, especially in the midline, has been cracked and crushed, and it is the least well preserved part".

I take a slightly different view concerning the mode of preservation of this specimen. After examining it I concluded that it was subjected to, and altered by, great pressures after

burial and before exposure. This major deformation of the skull, overlooked by Carney *et al.*, fundamentally affects the interpretation of the cranium. The maxillary part of the skull, although it is undoubtedly correctly fitted to the facial part of the fossil as far as the preserved specimen is concerned, has an altered relationship to the superior part of the face, compared with the presumed condition before burial. The present (post-burial) conformation of the partial cranium seems to be the result of not only lateral pressure, in addition to fairly extensive crushing, shown by the mosaic nature of the bone, but the palate was also pushed inferiorly and slightly anteriorly. This resulted in the alteration of the occlusal surface of the specimen compared with the preserved parts.

Carney *et al.* note (page 514) that the zygomatic process arises from a very anterior and a very inferior position from the maxilla, and they state that this "would have the effect of aligning the anterior attachment of the superficial fibres of m. masseter as tangential to the curve of Spee as possible". The zygoma of SK 13/14 also has its "roots" very low on the maxilla, approximately to the same degree as in KNM-CH-1, distinctly lower than the origins of the zygoma on SK 48.

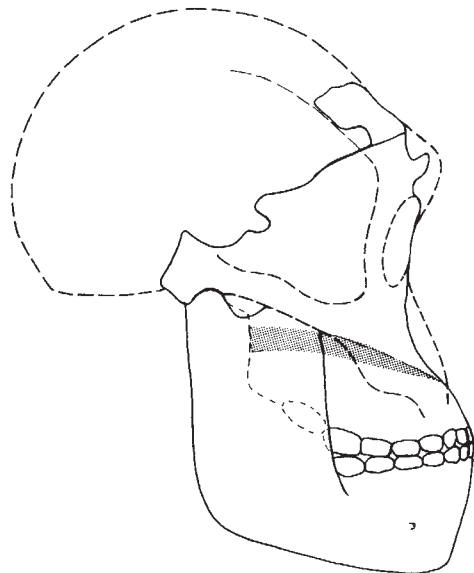


Fig. 1 Reconstruction of the Chesowanja robust australopithecine KNM-CH-1, as presented by Carney *et al.*¹, fitted with the corpus of the Peninj mandible from Lake Natron. The ramus was drawn after the teeth of the Peninj mandible were matched in size with those of the Chesowanja specimen. The stippled area on the cranium represents a segment of the fossil interpreted to be the result of deformation.

Carney *et al.* also state that the "postorbital constriction in KNM-CH-1 is not nearly as great as seen in the other robust australopithecine specimens". They do not mention that the veracity of this statement is dependent on, first, the lateral positioning of the frontal fragment as shown by these authors, and, second, on the assumption that all known robust australopithecines, regardless of sex, share the extensive postorbital constriction displayed by OH 5 and the various pertinent Swartkrans specimens. Before drafting their article, Carney *et al.* had the opportunity to examine the robust female cranium collected by R. E. F. Leakey².

Carney *et al.* imply a substantial brain increase for the Chesowanja robust australopithecine cranium. The frontal view in their Fig. 3 shows a reconstructed calotte which not only rises high above the brow ridges (following the line of the fitted frontal fragment), but is also laterally expanded, well beyond the proportions of any robust or gracile australopithecine. This figure can be compared with the stage represented by the Choukoutien loc. 1 hominids (Weidenreich's reconstructions, in the American Museum of Natural History) approximately 400,000 years ago. In addition to the recon-

struction, Carney *et al.* comment that "KNM-CH-1 has clearly much bigger anterior and middle cranial fossae than in Olduvai Hominid 5 or as seen in SK 1585 natural endocast". I have also made the comparisons but I could not arrive at an objective judgment because of the badly folded and crushed condition of the cranial fossae of KNM-CH-1.

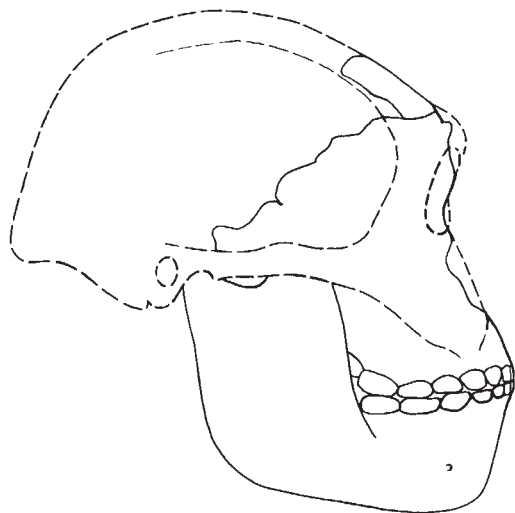


Fig. 2 New reconstruction of the partial Chesowanja cranium. The stippled area of Fig. 1 is excised and the frontal fragment is refitted. Matching the teeth of the Peninj mandible to those of the skull resulted in a perfect fit of the ramus into the space allotted by the reconstruction. This reconstruction of KNM-CH-1 closely resembles the female robust australopithecine KNM-ER-732 collected by R. E. F. Leakey².

To test my observations I fitted the reconstruction of Carney *et al.* with the horizontal ramus and dentition of the Peninj mandible. I then proceeded to add the ascending ramus according to the space allotted by the original reconstruction of the skull (Fig. 1). The resulting mandible has a substantially higher ascending ramus than either the Peninj or the SK 23 mandibles. I then prepared a reconstruction based on my interpretation of KNM-CH-1. This differed from Carney *et al.*'s reconstruction in having a slightly different orientation of the hemi-skull, the placement of the frontal fragment in a more medial position and the excision of a segment from the lateral profile shown by stippling in Fig. 1. This part of the skull, as noted earlier, represents what I believe was a part deformed by the movement of the lower face inferiorly and slightly anteriorly. I placed the frontal fragment above the brow ridges more medially than shown by Carney *et al.* in view of the presence of the median supraorbital depression. To this lateral cranial outline I then fitted the Peninj mandible and, in contrast to Fig. 1, the height of the ascending ramus then corresponded to the new facial height of KNM-CH-1. I fitted the mandible after the stippled segment of Fig. 1 was taken out of the lateral outline; the fitting was thus independent of the assessment of the degree and mode of deformation.

If correct, Carney *et al.*'s reconstruction of KNM-CH-1 suggests that besides an apparent great increase in the size of the brain, there was an increase in the distance between the plane of the tooth row and the plane of the temporomandibular joint. The Chesowanja australopithecine would thus be better equipped for herbivorous grinding than any known hominid. The relatively very small canines may be regarded as signs of extreme graminivorous adaptations, but they may also be indicative of the sex of the specimen. I prefer the view that the Chesowanja cranium is a female robust australopithecine, and that it does not show convincing evidence that it represents a large brained evolutionary lineage.

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Sampling Variation of Reported Results

BAKAN¹ suggests there is a relationship between birth order and lefthandness. Specifically, the high risk births (defined there to be the first born and the fourth or later birth) are more prone to be lefthanded.

A survey of 321 university students, made as a statistical exercise in the conducting of a sample survey, rather than for medical implications, is shown in Table 1. (The χ^2 values are calculated using Yate's continuity correction.)

Table 1 Handedness and Birth Order

Birth order	All		Male		Female	
	R	L	R	L	R	L
1, 4+ (high risk)	168	21	97	10	71	11
2, 3 (low risk)	115	17	69	7	46	10
	$\chi^2 = 0.09$		$\chi^2 = 0.05$		$\chi^2 = 0.22$	

The results are clearly not significant and do not support the hypothesized relationship between birth order and handedness.

This result is, in itself, unremarkable and the problem is whether it can or should be considered by itself. Surveys of this nature on this fairly simple idea or on closely related ideas may well have been carried out before, possibly frequently. Before discarding these results it is worth asking how many other sets of results have been similarly discarded, either because the research worker thought he was pursuing "an unprofitable line of research" or because an editor thought the results "uninteresting". If selection of results to be published operates, as to some extent it must, then reported results and particularly probabilistic statements referring to significance levels must be interpreted accordingly. If, for example, fifteen experiments are performed to detect a relationship which is not present, the probability that one or more experiments will give a result significant at the 0.05 level is 0.54.

How then shall the scientific world be kept informed of the weight of negative evidence? Some information is clearly necessary so that an estimate can be made of the bias in published significance levels. It is obviously impractical for journals to publish results of all experiments, whether positive or negative. A possible solution to the problem could be that where a journal publishes some results, short notes are en-

couraged about similar experiments, whether or not these have yielded positive results.

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¹ Bakan, P., *Nature*, **229**, 194 (1971).

Unusual Tonoplast in Conifer Leaves

I HAVE found a type of tonoplast in conifer leaves that has not been reported before. Its characteristics suggest that this plasma membrane may be involved in stress resistance in plant cells.

Leaves and bark cortex of various woody species were cut by hand with a razor blade into sections about 1 mm square and 100 μ m thick, prefixed in buffered (pH 7) 6% glutaraldehyde for 24 h, and then stained with either 5% KMnO_4 (pH 7) for 7 min at 20° C or 2% OsO_4 (pH 6.8) for 3 min at 7° C. Sections were passed through graded ethanol-water solutions to 100% dehydrated ethanol¹, then to propylene oxide, two changes of 15 min each, to propylene oxide-epon (1:1), and to epon (D.E.R. 332 and 732) as outlined by the manufacturer (Polysciences, Rydal, Pennsylvania). Thin sections were cut with an MT2 Sorvall ultramicrotome, mounted on uncoated copper grids, and observed with an RCA EMU-4A electron microscope using a 50 μ m objective aperture at 50 kV.

A layer, 0.4–1.0 μ m thick, between the main vacuole and the cytoplasm was observed in leaf chlorenchyma cells of *Picea pungens* Engelm. and *Juniperus virginiana* L. (Fig. 1). This layer is unusual because the tonoplast in higher plant cells, including those of woody plants, is generally recognized to consist of a single membrane (for example, ref. 2). Since the layer stains with OsO_4 as well as with KMnO_4 , lipid seems to be present³. No such layer was found in the living cells of the leaf stele. There was no apparent seasonal variation in the occurrence or thickness of the layer, which might be expected if it were related to seasonal changes in cold resistance. Heat treatment (57° C for 30 s in summer) disrupted the layer into irregular globules distributed along the outer edge of the main vacuole, again suggesting a lipid nature. The layer does not seem to be an amorphous mass or of artefactual origin, for it sometimes was bounded by a membrane on the vacuole (inner) side (Fig. 1, upper right). Another embedding procedure, using 'Vestopal'¹, also revealed the layer in spruce leaves.

A limited survey of other conifers, including *Pinus strobus* L., *Tsuga canadensis* (L.) Carr., *Taxus baccata* L., and *Thuja occidentalis* L. revealed the presence of a similar but thinner layer. In *Thuja* leaves, it was often lacking, and it was not present at all in leaves or bark of broadleaved trees such as *Fraxinus americana* L., *Ulmus americana* L., and *Acer saccharum* Marsh.

Somewhat similar tonoplasts, or layers adhering to the tonoplasts, have been observed in lower plants⁴, but not in higher (tracheophytous) plants, as far as I know. The fact that the layer is thickest in the two most drought-resistant species (*J. virginiana* and *P. pungens*) suggests that it may have some advantage for the leaf in water retention. When leaves

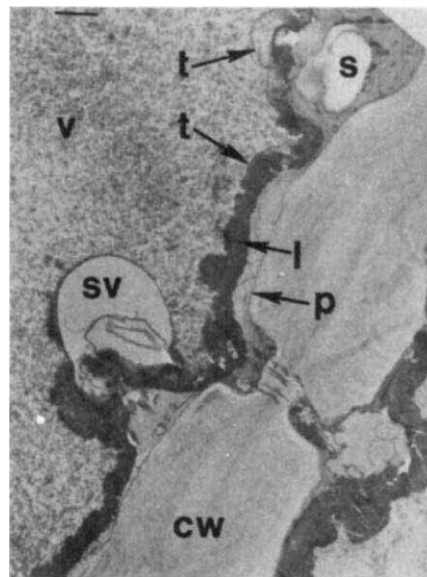


Fig. 1 Part of a chlorenchyma cell of *Picea pungens* together with part of an adjacent cell. l, Layer of lipid-like material; t, inner membrane (perhaps tonoplast) bounding lipid-like material; v, central vacuole; sv, small vacuole (an apparently similar one occurs below the pit, lower right); cw, cell wall (of two adjoining cells); p, plasmalemma; s, starch. A pit with plasmodesmata appears in the cell wall. KMnO_4 stain. Bar at upper left represents 1 μ m.

of these two species were slowly dried to 35% of the original fresh weight in 3 days, chloroplast lamellae and mitochondrial cristae often disintegrated or lysed while tonoplasts (including the thick layer reported here) usually remained intact. This supports the electron microscope findings in *Drosophyllum*⁵ and *Zea mays*⁶, which indicate the great sensitivity of cytoplasmic organelles to dehydration. All of this supports the old observation⁷ that the tonoplast can remain intact after injury to the cytoplasm.

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Localization of Nitrogen Fixation in *Anabaena*

THE function of heterocysts in blue-green algae has been controversial for some time; there are indications that these enlarged cells are the site of nitrogen fixation^{1,2}. But non-heterocystous blue-green algae may fix nitrogen if grown under low oxygen tension³, so that heterocysts are not essential for nitrogen fixation in these algae. According to a current hypothesis⁴, in aerobic conditions nitrogen fixation is confined to heterocysts, while in anaerobic or semi-anaerobic conditions the vegetative cells fix nitrogen as well. We have evidence to support this view.

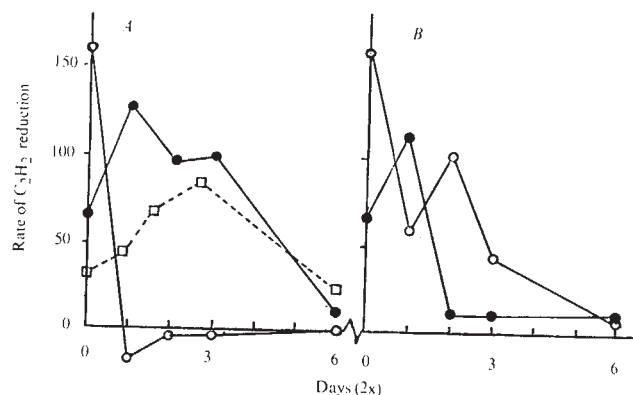


Fig. 1 Oxygen sensitivity of acetylene reduction after readmission of N_2 to an N -starved culture of *Anabaena*. A nitrogen-starved culture (grown under $H_2 + 5\% CO_2$ for 5 days) was incubated at $t=0$ under air + $5\% CO_2$ (A) and $N_2 + 5\% CO_2$ (B). Ethylene production was measured gas chromatographically after 30 min incubation of samples under air + $10\% C_2H_2$ (●), and under $He + 10\% C_2H_2$ (total). O_2 sensitive C_2H_2 reduction (○) is plotted as total minus O_2 resistant rate. Aerobic C_2H_2 reduction during the normal growth cycle of an aerobic culture (□) is also shown in A. Rate of C_2H_2 reduction was normalized on a chlorophyll basis

$$\left(\frac{\text{nmol } C_2H_2/\text{ml.}/30 \text{ min}}{A(680 \text{ nm}-740 \text{ nm})/\text{cm}} \right)$$

and plotted against time after readmission of nitrogen.

One of the first obvious effects of nitrogen starvation in blue-green algae is the disappearance of phycobilin pigments, which normally constitute about 15% of the dry weight. The continuation of some growth and chlorophyll synthesis during starvation suggests⁵ that phycobilins serve as a reserve source of nitrogen. We have studied the pattern of synthesis of one phycobilin, phycocyanin, after readmission of nitrogen to cultures starved of the element.

Cultures of *Anabaena cylindrica* (Cambridge Culture Collection No. 1403/2a) were grown in the medium of Allen and Arnon⁶, and gassed with 5% carbon dioxide in air. Phycocyanin was observed by its autofluorescence and absorption under the microscope. Fluorescence was excited with a high pressure mercury arc from which the 546 nm line was isolated by a filter combination consisting of Balzers Calflex C and Corning CS 4-96 (2) and CS 3-368. Phycocyanin fluorescence was isolated with a Balzers B-40 632 nm and a Schott AL 638 interference filter, transmitting a band of 7 nm halfwidth at 632 nm. In cells of *Chlorella* no fluorescence could be seen in these conditions, so chlorophyll fluorescence is negligible at this wavelength. The absorption image was studied with the filter combination used for isolating the fluorescence. A phycobilin-free culture was obtained by bubbling a normal culture with $H_2 + 5\% CO_2$ for 6 days.

If nitrogen was readmitted aerobically (5% carbon dioxide in air) most series of vegetative cells situated between two heterocysts showed a gradient in phycocyanin fluorescence after 20 h. Intensity was greatest in the cells adjacent to heterocysts and least about halfway between the heterocysts. Normal mature heterocysts do not fluoresce. The most evident fluorescence gradients corresponded to gradients in phycocyanin absorption, so that the results are due to differences in phycocyanin concentration and not in fluorescence yield in different cells. If these gradients are caused by differences in the availability of nitrogen, this experiment shows that in an aerobically grown culture of *Anabaena*, N_2 is fixed exclusively or predominantly in the heterocysts.

If N_2 was readmitted anaerobically (5% CO_2 in N_2), the rate of phycocyanin synthesis was the same but gradients in phycocyanin concentration were rare and far less pronounced than in

aerobic cultures. This indicates that in anaerobic conditions vegetative cells also fix nitrogen. It also seems that all cells reduce neotetrazolium in anaerobic cultures. After addition of ammonium phosphate, whether aerobic or anaerobic, no gradients of phycocyanin concentration develop during synthesis of the pigment.

An aerobic culture that was in the process of losing its phycocyanin due to molybdenum deficiency also exhibited concentration gradients. Here heterocysts appeared also in the regions with low phycocyanin content, alternating with heterocysts whose neighbouring cells had a high concentration of phycocyanin. This pattern indicates that these were young heterocysts, differentiated after molybdenum had been exhausted in the medium, and so unable to synthesize nitrogenase. This experiment confirms that the gradients in phycocyanin concentration are due to nitrogen deficiency and that nitrogen is fixed chiefly by the heterocysts. It also seems that molybdenum does not migrate from one cell to another in significant amounts.

Another consequence of the hypothesis is that it should be possible to distinguish nitrogen fixation by vegetative cells and by heterocysts on the basis of their oxygen sensitivity. The reduction of acetylene by anaerobic cultures is strongly, and in part irreversibly, inhibited by oxygen. In aerobic cultures inhibition by oxygen, if any, is completely reversible. In Fig. 1 the oxygen sensitive and oxygen resistant parts of acetylene reduction by the aerobic (A) and anaerobic (B) nitrogen-starved cultures are plotted as a function of time after readmission of the gas. The dotted line in Fig. 1A represents the pattern of acetylene reducing activity during the growth of a normal aerobic culture, which roughly parallels the growth rate. On the first 2 days after nitrogen starvation there is an extra acetylene reduction, which is also resistant to oxygen in the anaerobic culture (Fig. 1B). If oxygen resistant nitrogen fixation is located in the heterocysts, this may account for the few and indistinct phycocyanin gradients seen in the anaerobic culture.

Other arguments have been published as evidence that the heterocyst is the site of nitrogen fixation⁷. As Smith and Evans⁸ emphasized, the yield of acetylene reduction by isolated heterocysts was too low to permit any direct conclusions. Heterocysts reduce neotetrazolium to formazan crystals after removal of tetrazolium, and acetylene reduction was irreversibly inhibited in filaments in which the heterocysts contained formazan crystals. We found, however, that the formation of microscopically visible formazan crystals, but not the irreversible inhibition of acetylene reduction by neotetrazolium, can be prevented by 2 mM sodium azide during treatment with tetrazolium.

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BOOK REVIEWS

Coral Reefs

Atlantic Reef Corals. (A Handbook of the Common Reef and Shallow Water Corals of Bermuda, the Bahamas, Florida, the West Indies and Brazil.) By F. G. Walton Smith. Pp. xii+164. (University of Miami: Florida, August 1971.) \$6.95.

INTEREST in coral reefs is growing and the republication of this small book, which first appeared in 1948, is welcome. It deals with the coral fauna of the Caribbean and Gulf of Mexico with outlying populations as far north as Bermuda and as far south as the coast of Brazil. Many of the shallow water coral reefs in these areas are among the most readily available in the world, with increasing numbers of marine biologists and interested tourists wading, swimming and diving among the corals.

The shallow water coral fauna of the Atlantic is small enough for it to be largely covered in this small compass with adequate general descriptions and photographs of all common species. Some additions have been made to those originally described but the full list of Atlantic corals, including many from the lowest levels of reef growth, is now becoming considerable. This is largely due to the activities of the late Professor T. F. Goreau and those associated with him in Jamaica. These were to have been monographed by him in collaboration with Professor J. W. Wells of Cornell who will now, it is greatly hoped, proceed with other collaborators.

Where this book fails is in its account of living corals. For example, no mention is made of the mesenterial filaments, those extraordinary structures which wrap round and consume the animal prey within, or sometimes outside, the gastric cavity. The reader is merely told that food is digested by "the mesenteries". The zooxanthellae, endozoic algae the presence of which distinguishes the reef-building or hermatypic corals from the deep or cold water ahermatypic corals, receive bare mention. They are described as "blue green algae" to which they have never been ascribed. It has long been known that they represent vegetative stages of dinoflagellates; they are indeed imprisoned phytoplankton. Their supreme importance in speeding the rate of calcification—the basic difference between hermatypes and ahermatypes—which was experimentally demonstrated by Goreau is not even mentioned.

There is now so very much to tell the general reader about the life of corals that one can only regret that the opportunity has been missed. While I am perhaps flattered to have the

reader referred to my *Year on the Great Barrier Reef*, this has now been out of print for a quarter of a century and in any case is completely out of date. However, the reader will get a handy, well organized and illustrated description of all the Atlantic corals that he is likely to encounter.

C. M. YONGE

Forest Radioecology

A Tropical Rain Forest: a Study of Irradiation and Ecology at El Verde, Puerto Rico. Edited by Howard T. Odum and Robert F. Pigeon. Pp. 1,678. (US Atomic Energy Commission: Oak Ridge, Tennessee, 1970.) \$10.

SOME ten years ago the US Atomic Energy Commission, to meet the pressing need to know more about the effects of radiation on natural ecosystems, embarked on a broad programme of "forest radioecology". The object was to study the damage to forest communities from gamma radiation at intensities comparable with those which might be experienced in a major reactor accident or in the use of nuclear explosives in peace or war. Because different forests would probably not respond to radiation in the same way, it was necessary for studies to be made in more than one type of forest and in several clearly differentiated climatic zones.

The experiments at Brookhaven and elsewhere in the continental United States are well known and have given much useful information on radiation damage in pine and broadleaved forests in a temperate climate. Here, in this huge volume, are the results of investigations carried out since 1963 in evergreen tropical forest in the West Indian island of Puerto Rico. The choice of Puerto Rico had several advantages—it was US territory and easily accessible; the El Verde Experimental Forest, some of which was still in an almost "virgin" condition, was available, and the Puerto Rico Nuclear Center was close at hand. It was a disadvantage that this forest is montane and, being in a hurricane belt and on an island, was in several respects different from the "classical" lowland rain forest of Amazonia or Malaya; conclusions drawn from El Verde may not apply to rain forests elsewhere.

Though the radiation experiment was its *raison d'être*, the El Verde project developed into an extremely wide-ranging study of the rain forest ecosystem as a whole: hardly any aspect or any of its component plant or animal groups was neglected. A vast army of investigators cooperated in the project and ninety-one of them have contributed

to this book. The resources of the Atomic Energy Commission made it possible for new methods and a great variety of expensive equipment to be tried out—even to enclosing part of the forest in a giant plastic cylinder 67 feet high and 60 feet in diameter. The 111 chapters in which the results are recorded vary greatly in importance: some are mere progress reports but others add notably to knowledge of rain forest ecology.

To put the Puerto Rico studies in perspective, work was also carried out in Dominica (which has a forest dominated by *Dacryodes excelsa* very similar to that at El Verde), at Panama and elsewhere.

To review critically the contents of a book such as this is hardly possible. Though the themes of energy utilization and the mineral cycle run throughout the book and Dr Odum in a final chapter entitled "An Emerging View of the Ecological System at El Verde" makes a courageous attempt to integrate the results, the appreciation of such a mountain of information requires time and experience beyond the resources of a single individual.

It may indeed be doubted whether the radiation experiment itself, important as was its aim, was the project's chief accomplishment. For practical reasons it could not be replicated and, because the treatment was not identical, it is not possible to make exact comparisons with Brookhaven and other sites. The results are not clear cut, though they seem to indicate that the tropical forest is less radiation-sensitive than that at Brookhaven.

On the other hand, the new insights into the rain forest as a functioning ecosystem are a great gain and will be studied with profit for a long time to come. Here for the first time can be found quantitative data on such subjects as the holes made in leaves by herbivorous insects, the half-life of leaves (four to nine months in most species) and a mass of interesting information about the roots and buttresses of tropical trees. Particularly fascinating are Odum's chapter on rain forest structure and mineral cycling homeostasis and such sidelights as the evidence for the part played by epiphyllae in the mineral cycle. A first attempt has been made to determine the age of a tropical tree by radiocarbon dating of the heartwood (370 ± 150 years in *Dacryodes excelsa* in Dominica).

If this book, in the hackneyed phrase, is chiefly a mine of information, one could perhaps ask for the miner's task to be made easier. Was it necessary to

bind the 1,678 pages into a single volume or even to bind them at all? At \$10 the book is a good buy, but a collection of separate articles would have been more comfortable to read than a volume measuring 28×22×6.5 cm and weighing nearly 5 kg. Reference would be easier if the number of the chapter and the author's name had been put at the head of each page.

Though the organization of the book is unsatisfactory, one can be grateful for the new knowledge it contains. No rain forest has ever been studied so intensively as El Verde. It is a pity that it requires the threat of nuclear disaster to make such a project possible.

P. W. RICHARDS

Excitable Cells

The Physiology of Excitable Cells. By D. J. Aidley. Pp. ix+468. (Cambridge University: London, June 1971.) £5.80; \$15.

PERHAPS every scientist considers that the recent history of his own discipline is the best demonstration of the scientific method in operation. That many neurophysiologists are of this opinion is understandable after reading D. J. Aidley's book, *The Physiology of Excitable Cells*, for this is a collection of elegant and intellectually satisfying experiments and analyses which, taken as a whole, contribute greatly towards an understanding of the fundamental workings of the nervous system.

After a brief introduction which deals with the concepts and techniques particular to the electrophysiologist, the book can be divided into three principal sections. The first concerns the neurone and the structure and electrochemistry of the cell membrane, both in the resting condition and during the propagation of the action potential. This is followed by a consideration of the neuromuscular junction and the physiology and pharmacology of synaptic transmission. The second section develops the subject of muscular contraction, building up from the essential structure of the myofibril and the coupling of the processes of excitation and contraction, to a study of the activity of entire muscles. The third section begins with a statement of the general principles that apply to the functioning of sensory receptors and the principles are then illustrated by reference to special sensory systems. These systems are the acoustics-lateralis system of vertebrates, mammalian muscle spindles, insect chemoreceptors, electroreceptors and the vertebrate eye.

The scope of the author's approach is impressive and has certainly involved the unenviable task of assimilating a great variety and depth of source materials. The result is a text written in an economical style which develops

the various themes in a logical and, for the most part, highly coherent way. The many mathematical arguments involved are well presented and adequately explained, the value of hypotheses is carefully weighed and the evidence for them is discussed in a good critical manner. In addition a genuine attempt has been made to develop a comparative approach so that various classical preparations, such as the squid giant axon, are placed in their proper comparative perspective and the inclusion of chapters on the electrical properties of glial cells and the physiology of the electric organs of fish enhances the impression of a well rounded account.

One small criticism is that the section on sense organs would not suffer from some expansion, nevertheless, this book more than fulfils its intention of being a course book for undergraduate students of neurophysiology and its comprehensive nature and critical style place it in favourable comparison with respect to other, and usually more restricted, works on the subject.

JOHN A. PATTERSON

DMSO Re-evaluated

Dimethyl Sulfoxide. Vol. 1: Basic Concepts of DMSO. By Stanley W. Jacob, Edward E. Rosenbaum and Don C. Wood. Pp. xv+479. (Dekker: New York, February 1971.) \$27.50; £13.10.

HERALDED as a new "wonder-drug" in 1964 and then condemned as dangerously toxic in the following year, dimethyl sulphoxide (DMSO) has been one of the most controversial chemicals of modern times. Although first prepared nearly a century earlier by Alexander Saytzeff, it was Stanley Jacob's and Robert Herschler's discovery of its unique tissue penetrating powers and its diverse pharmacological activities which led to the widespread interest in DMSO, particularly for its use as a solvent vehicle which enhanced the percutaneous absorption of drugs and for the many potential clinical applications in human and veterinary medicine and in agriculture. But reports of toxic effects to the lens of the eye in experimental animals (which have not been reproduced in man or primates) led the US Food and Drug Administration to terminate promptly the clinical investigations on the drug which were just getting under way. Many scientists, particularly Drs Stanley Jacob and Chauncey Leake in the United States and Dr Gerhard Ludahn in Europe, held faith with the new drug and subsequent work has indeed shown that the early reports of toxicity may have been exaggerated and the cessation of clinical studies was perhaps unwarranted.

Some five or more years later, the initial over-enthusiastic acclaim of its

potential as a drug and the following hasty condemnation have now given way to a more reasoned attitude with critical scientific evaluation replacing emotional subjective opinion, and the possible clinical uses of this interesting compound are being re-examined. The time was therefore most opportune for the publication of this evidence in its entirety and this is the stated intention of the editors of this encyclopaedic monograph on DMSO. In this first volume Stanley Jacob and his colleagues Edward Rosenbaum and Don C. Wood have brought together their own extensive published work on the subject and, along with that of many collaborators, have produced an impressive work of reference which covers the chemistry, biochemistry, pharmacology and toxicology of DMSO together with its radioprotective and cryoprotective properties and its uses in enzymology, microbiology, immunology, dermatology and veterinary medicine. This was no small task, for the published literature on DMSO is extensive, as may be adjudged from the number of references cited, which is well over two thousand. Somewhat regrettably, however, there is duplication of many of these in the last chapter entitled "DMSO Bibliography" which, for no stated reason, is confined to cryobiology, chemistry and pharmacology.

Nevertheless, this is an outstanding work of dedication by scientists and clinicians who believe in the future of DMSO. It is excellently presented and lucidly written and it will form the standard work of reference of the subject for biomedical scientists of all disciplines. The second volume of this monograph will contain reviews of the clinical studies on DMSO and it is to be hoped will present some of the most vital evidence of this controversy and thus complete the case for the reinstatement of DMSO as a useful agent in clinical medicine.

DENNIS V. PARKE

Camera in the Gut

The Digestive System. By P. G. Toner, K. C. Carr and G. M. Wyburn. Pp. x+303. (Butterworth: London, July 1971.) £10.

THIS book presents a timely synthesis of form and function in the alimentary tract and should have a wide appeal not only to basic scientists but also to gastroenterologists who seek a cellular background to their speciality. Written by a pathologist and two anatomists, the book surveys the normal cellular anatomy of much of the digestive system at the electron microscope level. Individual organs are not considered as single entities; the emphasis is on the various types of epithelial cell from

the oesophagus downwards. There is a section on mucosal architecture and cell renewal in the small intestine illustrated by optical and scanning electron microscopy, the latter providing a dramatic three dimensional surface view of the pattern of crypts and villi. Other regions of the tract are unfortunately not shown in this way. Salivary gland cells are considered, together with those of the liver, gall bladder (but not the bile duct), pancreas and Brunner's glands, and there is a final short chapter on non-epithelial components.

There are some 200 illustrations depicting both human and laboratory animal material. The prints are of a kind that most photographers would regard as "contrasty", but this is not meant as an adverse criticism, for they are of a generally high quality (the worst is the very first!). The legends are fully explanatory and their layout on the text page is pleasing. The text itself makes easy reading and the description of each cell type leads up to the all-important point—the correlation between structure and function, with suitable comment on those areas where current knowledge is sparse. There is a good summary of the endocrine cell problem as it existed at the time of going to press, but almost every month now brings new information on the cells that produce gastrin, secretin and other intestinal hormones, and no book can capture the latest word on this subject at present. There are useful reference lists, including an up-to-date addendum. An occasional typographical error has escaped the proof readers.

This volume is a significant contribution to the literature of gastroenterology and it is hoped that one of its effects will be to stimulate collaboration between clinician and basic scientist. Such rapport can bring nothing but good—provided that each recognizes the problems and limitations of the other in their respective fields of investigation. A book of this kind makes electron microscopy look all so easy, and many clinicians especially do not appreciate the amount of time and effort that has to be expended to obtain one good photomicrograph, let alone two hundred.

R. M. H. McMINN

Primary Battery

The Primary Battery. Vol. 1. By George W. Heise and N. Corey Cahoon. (The Electrochemical Society Series.) Pp. xvi+500. (Wiley: New York and London, April 1971.) £12.

It is more than twenty years since G. W. Vinal's well known book on primary batteries was published. In this time a commercial demand has been established for $\text{MnO}_2/\text{KOH}/\text{Zn}$ and $\text{HgO}/\text{KOH}/\text{Zn}$ batteries, and $\text{AgO}, \text{Ag}_2\text{O}/\text{KOH}/\text{Zn}$ batteries have

proved important for special high power density applications. Fuel cells have caught the public imagination for their role in space exploration and their potentiality in electric cars. These batteries, the Leclanché battery and other novel systems have benefited from considerable funds supplied by governments and private industry over two decades of intense activity and electrochemical awareness. A new book is clearly overdue. Indeed, almost a generation of battery technologists has matured and deplored the absence of a modern reference work to ease the task of assimilating existing knowledge.

Although the book under review is only the first of two volumes, the authority and care taken in compilation make clear that the work will be one of importance. The criticisms that follow are not intended to detract from this overall conclusion.

The historical introduction is by George W. Heise and the periods up to 1880 in particular are well done with events shown as a logical train rather than as a series of random happenings. It is regrettable that the period 1880–1920 which contains the origins of the important Leclanché dry cell is only dealt with sparsely. Heise himself must be uniquely placed to review this important era.

The chapter on fundamental aspects by Ernest B. Yeager and Eugene P. Schwartz with appendices comprises 22 per cent of the book. It is carefully worded, helpfully slanted in directions of battery interest and written to be understood. Apart from useful experimental advice on techniques, circuits and equipment, much of the content is available elsewhere in standard electrochemical texts. The electrode-solution interface is treated in depth and, while this is the heart of the battery process, fundamental instruction is also required on electrolytes, the solid state, separators, mixing, mixtures, particle technology and porosity, which are not considered. There seems little reason to include twelve pages of standard potentials derived from well known reference works, particularly since many are not relevant to primary batteries and those which are are given in another form in a further appendix. In the further appendix the data for the Leclanché cell are of doubtful value since Mn_2O_3 is represented rather than MnOOH .

The next six chapters, "Primary Cells with Caustic Alkali Electrolyte", "The Alkaline Copper Oxide: Zinc Cell", "Zinc: Oxygen Cells with Alkaline Electrolyte" all by Erwin A. Schumacher, "The Mercuric Oxide: Zinc Cell" by Samuel Ruben, "The Silver Oxide: Zinc System" by Thedford P. Dirkse and "The Alkaline Manganese Dioxide: Zinc System" by N. Corey

Cahoon and Harry W. Holland, are the *raison d'être* for this volume. These batteries are all made industrially for profit and fulfil a useful function in society. The treatments are adequate but except for the chapter on zinc: oxygen cells one is a little disappointed in their brevity. Ruben, for example, modestly dismisses his important invention in around 3,000 words. Something has gone seriously awry with tables 3.1 (page 171) and 3.2 (page 176). Clarification is needed to avoid any impression that Mn_2O_4 is involved in the initial open circuit voltage of $\text{MnO}_2/\text{KOH}/\text{Zn}$ cells (page 239) or that the cited degrees of on-load voltage stability for $\text{HgO}/\text{KOH}/\text{Zn}$ cells are achieved if MnO_2 is incorporated into the cathodes (pages 213, 214).

The final four chapters attain a very high standard. In "Fuel and Continuous Feed Cells" Ralph Roberts has summarized an immense amount of development effort in a concise and balanced account. Advances are shown without losing sight of the real objectives and the very considerable problems that still remain. "Low Temperature Non-aqueous Cells" by John M. Freund and William C. Spindler is instructive and readable. "Semidry and Solid-Electrolyte Batteries" by John N. Mrgudich and Demetrios V. Louzos is a stimulating chapter which gathers together for the first time much information in a logical and digestible form. Finally, Walter J. Hamer has built on the solid foundations laid in Vinal's book to produce a discussion of "Standard Cells" and related aspects that is excellent in all respects.

F. L. TYE

Biochemistry of Babies

The Biochemistry of Development. Edited by Phillip Benson. Pp. v+273. (William Heinemann Medical Books: London; J. B. Lippincott: Philadelphia, 1971.) £3.25.

THERE is a type of publication, with which all biologists are familiar, in which a handful of indifferent papers are mixed with a little elementary biochemistry, inadequately edited, given a grandiloquent title and a fancy cover, graced with a blurb or preface which explains that they are essential reading for all practising frothblowers, published at an exorbitant price and sold at a handsome profit to institutional libraries. In spite of some striking superficial resemblances Dr Benson's book does not belong to this depressing category. Behind its general and rather misleading title it is a collection of essays on the narrow but important and exciting theme of the biochemistry of the foetus and the newborn mammal. Although the chapters are numbered as though they formed part of a continuous exposition they are quite independent of

one another. They deal, at varying levels of specialization, with a wide variety of topics. The core of the book is formed by five chapters which together form a fairly coherent account of the general biochemistry of the foetus, of the biochemical changes which accompany its development, and of the dramatic biochemical readjustments which take place when it is born. The treatment is rather uneven. The lipid chapter, for example, includes a higher proportion of elementary and general material than the others. The chapter on urea biosynthesis, at the other extreme, seems to be based largely on the author's own experimental results. Dr Benson's own chapter starts with a review of the regulation of genetic expression but incorporates a quite detailed account (with numerous figures) of his own experiments. The remaining chapters deal with more isolated topics: the regulation of foetal liver development; the intrauterine diagnosis of inherited disease; foetal haemoglobin; the autacoids; and polymorphism in human proteins.

Considered as a collection of biochemical essays the book has substantial merits. The topics with which it deals are intrinsically interesting and not perhaps sufficiently well known to biochemists. Though the contributors vary so much in their approach, the quality of their contributions is generally high. Their variety itself is an advantage to the casual reader. It is perhaps too strictly biochemical in its approach and too full of biochemical technicalities to be readily intelligible to most of the paediatricians and obstetricians to whom it is apparently addressed. But almost any intelligent student of biochemistry is likely to read at least some of the chapters with interest and enjoyment. For a work addressed to a fairly specialized audience and therefore with limited circulation, its price is surprisingly reasonable.

R. Y. THOMSON

Soviet Rocketry

Soviet Rocketry: The First Decade of Achievement. By Michael Stoiko. Pp. xi+272. (David and Charles: Newton Abbot, August 1971.) £3.25.

It would, perhaps, be better to call this book something like "A Kremlino-logist's Notes and Thoughts on Soviet Rocketry". The first chapter (pages 1-16) gives a sketchy outline of the early history of rocketry in the world, but contains several factual inaccuracies. The second chapter (pages 17-24) is called "Tsiolkovsky's Legacy", but no analysis of his historic contributions appears. On page 18 we meet the old acquaintances: "he mastered mathematics *first* and *then* physics", and "in

1881 he began his first serious scientific research in *three areas*—all-metal dirigibles, airplanes and rockets".

Tsiolkovsky wrote his famous letter not to the Central Committee of the Communist Party (page 24), which is a post-cult-of-personality formulation, but to the great teacher and leader I. V. Stalin, whose address was the Central Committee.

On page 26 we read that "Tsiolkovsky's chief contribution lay in his conclusion that the only possible means of flight in space must be based on the reaction principle. . . ." I think that this is a somewhat untidy formulation since (1) the reaction principle was known to and had been used by man centuries before Tsiolkovsky was born; (2) Tsiolkovsky's collected works, especially his *Album of Space Travel*, show that the range of his contributions to rocketry and space travel was very much wider than the reaction principle; permanent orbital stations, regeneration of biological waste in space, energy problems in free space, space walk, space plants—all these and many other subjects were studied by him quite rigorously.

Chart 1 on page 32 ("Evolution of Soviet Rocket Societies") contains factual mistakes (the positions of Tsander, Korolyev and Kostikov, GIRDs throughout the USSR). The statement that after the formation of the Zhukovskiy Academy "at least fifteen comparable academies of astronautics have been built" (page 30) is wrong; one can guess that the author intended to say "fifteen *military* academies", which is a different thing. Statements such as "during the years 1928-30 *numerous* rocket conferences were held" in the USSR, "GIRD became *national* in scale with branches in *major cities*" (page 47) and a "Rocket Research and Development Centre" (page 47) was established in 1932 at 19 Sadovo-Spasskaya Street are obvious exaggerations conflicting with facts. And certain remarks about M. K. Tikhonravov and V. P. Glushko (page 62) do not hold water.

Chapter 6 ("Prelude to Sputnik") describes rocket work in Germany and the Soviet Union up to August 1957. The rest of the book deals with the now well known Soviet space achievements and attempts to outline their organizational skeleton; the principal facts are described accurately, the illustrations are good, but up to thirty inaccuracies and mistakes of varying importance have been noticed.

The gloomy warnings by Richard Nixon (then Vice-President) on October 16, 1957 (that Sputnik 1 was "a grim and timely reminder" to the United States) and by Vice-Admiral Hyman G. Rickover in 1961 (that "the United States and Russia are not engaged in a popularity contest but in a grim techno-

logical race") seem to be irrelevant and unnecessary. The somewhat *à vol d'oiseau* foreword by Patrick Moore confuses Russia with USSR and vice versa.

No sources of information are given anywhere, but a bibliography is available at the end of the book.

G. A. TOKATY

Eastern Libraries

Libraries in the East: An International Comparative Study. By George Chandler. Pp. 214. (Seminar: London and New York, 1971.) £2.50.

INFORMATION about the development of libraries and librarianship in the East is scattered throughout Unesco and other report literature, or appears in short articles in the periodicals of the countries concerned. Thus it is difficult to obtain a complete picture and especially to study progress on anything like comparable terms. The present book aims to survey the recommendations which have been made at Unesco seminars on the development of library services in the East and to compare the advances in eight Eastern countries (the Lebanon, Egypt, Iran, Pakistan, India, Thailand, Hong Kong, and Japan) as seen at first hand during a tour by the author as president of the International Association of Metropolitan City Librarians (INTAMEL). The countries are taken in turn and considered under such headings as the structure of the library services, library associations, schools of librarianship, national libraries, documentation centres, and, where appropriate, public, special and academic libraries.

Inevitably coverage is variable because it is limited almost entirely to institutions visited on the tour made in 1970. It is admitted that, where certain libraries are selected for detailed consideration, though the intention was to reflect general problems for the East as a whole, choice in the last analysis was personal or even accidental, depending on the information provided by the librarians of the libraries visited. Nevertheless, we are appreciably further forward in knowledge of Eastern libraries and indebted to Dr Chandler for presenting the information gained on his tour in the constructive framework of a comparative study. Many readers will wish that personal impressions of each country's library development were given much more space and prominence. These "conclusions", which are limited to six or seven lines of text, do not appear for every country. An appendix provides a select bibliography of Eastern libraries, covering the period 1950-1970, and a second appendix reprints a survey of library service in Asia prepared for Unesco in 1967.

WILFRED ASHWORTH

CORRESPONDENCE

Preserving Rare Breeds

SIR,—I was interested to read your report, "Keeping Fossils Alive", of a conference on "rare breed survival" which was held on October 15. This correctly refers to the fact that rare breeds of cattle, sheep and poultry had been kept as a "gene bank" at Whipsnade, but is wrong in saying that the animals "had to be dispersed when the Zoological Society of London needed the space".

The story is as follows. On a decision taken by the Society's council, small flocks and herds of rare native domesticated breeds were collected and established at Whipsnade in 1961 with the object of preserving them, not merely as historic remnants, but as material for study by geneticists, physiologists and other scientists. An offer to put the animals at the disposal of *bona fide* investigators and to collaborate in their research projects was made in your

journal in 1964². A useful study of the blood groups of sheep was carried out by Tucker³; otherwise the response to our offer was disappointing, and we failed either to stimulate interest or to obtain financial support for the appointment of scientists to our own staff to study these animals.

After exchanges with other scientific bodies, and following much deliberation by its scientific committees, the council of the Society was advised that greater use might be made of these valuable stocks if they were transferred to agricultural institutions where they would attract the interest of students, and where better facilities for rearing the young would be available.

Accordingly, in 1968, flocks of three breeds of sheep were transferred to Professor Bowman at the School of Agriculture, University of Reading. Arrangements were made with Mr Christopher Dadd, Director of the National Agricultural Centre, for the transfer of the

remaining four breeds of sheep to Stoneleigh Park, Kenilworth, where they have now attracted considerable public interest. In 1970, the NAC was also presented with surplus animals from the Zoological Society's herd of Chartley Cattle at Whipsnade.

What I should like to correct is the statement that the Society dispersed the gene bank it had established on its own initiative because "space was needed". The animals were sent to institutions where it was hoped they would attract more interest than they had done at Whipsnade and where they would consequently be of greater value to agricultural science.

Yours faithfully,

LORD ZUCKERMAN

Secretary

Zoological Society of London,
Regent's Park, London NW1 4RY

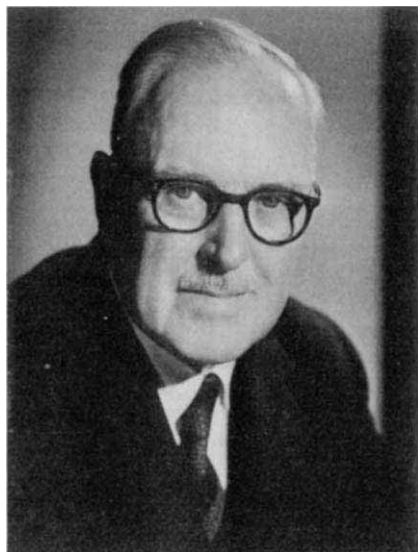
¹ *Nature*, **233**, 587 (1971).

² Rowlands, I. W., *Nature*, **200**, 131 (1964).

³ Tucker, E. M., *Nature*, **216**, 684 (1967).

Obituary

Sir Ernest Marsden



[Photo by Walter Bird]

ERNEST MARSDEN, who died at the end of last year, was born at Rishton, Lancashire, on February 19, 1889. His mother had a hardware shop, selling cooking utensils, nails and similar goods. Ernest was one of four sons, and helped in the shop from time to time. In the school holidays he used to go to his aunt's at Blackpool, where he helped with washing up, cleaning knives

and peeling potatoes, to earn pocket money. After attending the local school at Rishton, where he had already exhibited ability, he was sent to the Grammar School at Blackburn.

In 1906, when he was eighteen, he enrolled in the department of physics at Manchester University. Schuster and Petavel were still professors, and in 1908 he began research in atmospheric physics under Petavel. With the arrival of Rutherford in that year he changed to atomic physics. In 1909 Rutherford assigned him to assist Geiger in research on the scattering of α -particles. Before he had graduated, and before he was twenty years old, Marsden collaborated in the crucial experiment from which Rutherford established the nuclear structure of the atom. Five years later, pursuing Rutherford's general plan of exploring the collision of swift particles with matter, Marsden observed that when α -particles were projected into hydrogen, a few of the hydrogen nuclei were knocked forward far beyond the range of the α -particles.

His brilliant work and general capabilities caused Rutherford to recommend him for the most important chair of physics in his native land, at Victoria University College, Wellington, New Zealand. Marsden was appointed at the age of twenty-five. Rutherford asked

him whether he would mind his taking over the experiments on the impact of α -particles on hydrogen gas. In the following two years, during the First World War, Rutherford continued these experiments; by 1917 he had evidence that protons were being ejected from atoms—that the artificial disintegration of the atom had been achieved. Thus Marsden contributed to two of the most significant experiments in modern physics. In the early work on large-angle scattering, Marsden perceived that his observations implied that the atom might have a nuclear structure. But he was too young to have the confidence, or to have acquired the scientific knowledge and maturity, to put the idea forward and prove that it was true. The full force of Rutherford's genius was needed to do that.

In stature Marsden was short and stocky. He had the physique and liveliness of the Lancashire man of his period, and he spoke with the local accent. He was a Lancashire lad, generally referred to as "Ernie" behind his back, a typical descendant of the people who had done so much to create the industrial revolution, with their combination of intelligence, ingenuity and enterprising common-sense. Like his great master, Rutherford, he had a feeling for people, and inspired them by his genuine interest in their concerns,

however bluff his comments might be.

Shortly after arriving in New Zealand in 1915, Marsden was commissioned in the New Zealand Engineers. He was seconded to the 1st NZ Expeditionary Force, and embarked for Europe in 1916. He served with distinction in the development and operation of sound-ranging, being twice mentioned in dispatches, and was awarded the Military Cross.

After demobilization in 1919 he returned to his chair. He taught the varied collection of Wellington students with a natural enthusiasm and love of his subject, and persuaded the authorities to build a handsome new laboratory.

Almost as soon as he had launched these developments in physics his human as well as his scientific qualities attracted the attention of the Government. In 1922 he was appointed Deputy Director of Education in New Zealand. He became involved especially in matters connected with science. The need for the systematic organization of scientific and industrial research had become patent, so, in 1926, the New Zealand Department of Scientific and Industrial Research was set up, with Marsden as its first Secretary. He organized the first industrial research associations, promoting research over a wide range of sciences including physics, chemistry, geology, and food and agriculture problems. He inspired the harnessing of thermal energy from the ground, as well as the investigation of the causes of cracks in cheese, poor spreadability in butter, the control of weeds, poor baking quality in wheat, deterioration in frozen meat and chilled fruit cargoes to Britain. During the depression of 1933–39 he stimulated the application of geophysics to the development of New Zealand mineral resources, and new possibilities for the utilization of plant and animal products. Among the successful subjects of re-

search were the treatment of bush sickness, the quality of wheats, and the transport of beef.

In the Second World War Marsden had the leading part in adapting and developing New Zealand's scientific resources to meet the situation. He expanded the Dominion Physical Laboratory, and promoted research in submarine detection. The Radar Development Laboratory which he established supplied US forces in the Pacific with 110 radar sets before these could be provided from home American sources. He originated the Defence Science Corps.

Marsden naturally became the chief representative of New Zealand science on the national and international scene. He became a familiar and much respected figure as Scientific Liaison Officer in London, both in military and civil matters. In 1947 he was appointed New Zealand Government Scientific Adviser in London. As such, he became the chief New Zealand representative in the post-war United Nations scientific developments.

Marsden retired in 1954, but continued an active scientific life up to his seventy-seventh year. He became particularly interested in bioradiation and cancer research. He believed that radioactivity inhaled from tobacco smoke was a cause of lung cancer, the radioactivity being derived from the soil in which the tobacco had been grown.

Marsden was elected a Fellow of the Royal Society in 1946, and President of the Royal Society of New Zealand in 1947. He was knighted in 1958. He received many scientific awards and distinctions, but one which he very specially valued was his presidency of the Rutherford Jubilee International Conference at Manchester in 1961, in celebration of the fiftieth anniversary of the demonstration of the nuclear theory of the atom.

In 1913 Marsden married Margaret Sutcliffe. They had a son and a daughter, both of whom are in New Zealand. He married Joyce Winifred Chote in 1958. He died on December 14, 1970.

Errata

The review in last week's *Nature* by Lancelot Law Whyte "Science and Synthesis" (*Nature*, 234, 159; 1971) was unfortunately published under the wrong bibliography. This should have been as follows: *Science and Synthesis*. (An International Colloquium organized by Unesco on the Tenth Anniversary of the Death of Albert Einstein and Teilhard de Chardin.) Pp. vii+206. (Springer: Berlin and New York, 1971.) 38.50 DM; \$10.50.

In the article by E. A. Barnard, J. Wiekowski and T. H. Chiu on page 207 of this issue, the manuscript was received on June 23 and was not revised as stated.

International Meetings

December 7, **The Determination of Non Metals by Atomic Spectroscopy**, London (Society for Analytical Chemistry, 9–10 Savile Row, London W1X 1AF).

December 14, **Financial Control of R and D**, London (Science Policy Foundation, Benjamin Franklin House, 36 Craven Street, London WC2N 5NG).

December 15, **Public Participation in Highway Planning**, London (Institute of Civil Engineers, Great George Street, London SW1).

December 17, **Applications of Vibrational Spectroscopy to High Polymers**, London (Dr W. O. George, School of Chemical Science and Technology, Kingston Polytechnic, Penrhyn Road, Kingston upon Thames, Surrey).

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